RU 486: THE IMPORT BAN AND ITS EFFECT ON MEDICAL RESEARCH

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RU 486: THE IMPORT BAN AND ITS EFFECT ON MEDICAL RESEARCH

MONDAY, NOVEMBER 19, 1990

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND ENERGY,
COMMITTEE ON SMALL BUSINESS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:08 a.m., in room 2359-A, Rayburn House Office Building, Hon. Ron Wyden (chairman of the subcommittee) presiding.

Chairman WYDEN. Good morning. Today, the Subcommittee on Regulation reviews the June 1989 decision of the United States Food and Drug Administration to ban the importation of the French drug RU 486 for personal use. Specifically, the subcommittee will inquire into the effect that this ban has had on American medical research and the approval of new drugs in the United States that may have multiple benefits.

Few recent drugs have generated as much interest as RU 486. The drug is considered a success in France as an alternative to surgical abortion. Many scientists now believe that the drug can successfully treat debilitating and life-threatening illnesses such as breast cancer, brain cancer, diabetes, and Cushing's Syndrome. According to published reports, both western industrialized nations and the Third World are now testing RU 486 in various trials and, in some cases, to distribute the drug.

But the response of United States health authorities to RU 486 has been markedly different and resistant. The FDA has banned the importation of the drug for personal use on the grounds that RU 486 is a health hazard threatening the safety of the user.

What proof does the agency have to back up its conclusions about RU 486? To answer this question, subcommittee staff spent almost a year investigating the FDA's documentary evidence. FDA files—the legal foundation for the import ban—are notable for what they contain and for what they lack.

The subcommittee asked, for example, if the FDA believed there was an active black market in this drug—a good reason for imposing a ban. But apparently there is nothing in the file which remotely justifies this concern. In fact, RU 486 is sold by prescription only, and then administered only in a tightly controlled, precertified clinical environment. This is simply not like buying a bottle of aspirin.

The FDA has been unable to produce any evidence that the manufacturer's tight controls on this drug have been anything less than completely successful.

The subcommittee asked if there were any documents in the file, letters from FDA field offices or United States Customs offices, warning that surreptitious importation of the drug had occurred. Again, the file drawer was empty.

The subcommittee asked if the FDA had any record of seizures of the drug. A document in the file, dated January of this year, written by an FDA official, says that going back 2 years there is no evidence of RU 486 seizures.

The subcommittee asked if the FDA had done any research regarding the drug's safety. There is nothing in the file. But in France, where more than 65,000 women have taken the drug during the last few years, the RU 486 safety record is very strong. Let me summarize.

According to the FDA files there are: One, no records of injuries due to the drug; two, no records of a black market, foreign or domestic; and three, no record that there has been any attempt to import the drug into the United States. Nevertheless, the FDA has concluded that this drug is a health hazard. Why or how, we don't know.

Let us turn to what is in the FDA file. For the most part, it is filled with letters and correspondence from antiabortion activists and their allies in Congress. These communications are remarkable both for their character and their timing. It would seem when certain folks pressed FDA's button, the FDA was only too happy to respond quickly. For example, only 19 days elapse between one particular high-level, congressional demand on FDA to stop personal importation of the drug and the RU 486 import ban. This certainly has to be a new land-speed record for an agency response to congressional inquiries.

The Chair believes that the FDA's basis for restricting the personal importation of RU 486 is especially important for two reasons: First, the June 1989 decision is the first major policy statement on the part of the United States Government as to how it views RU 486; second, shortly after the FDA's decision, critical research not related to abortion using RU 486 slowed down, or came to a halt.

Perhaps the best example of this research slow down involves the National Institutes of Health study for treatment of Cushing's Syndrome. This devastating, and sometimes fatal, disease has responded remarkably to treatments using RU 486. NIH researchers will tell us today that this is nothing less than a medical breakthrough. They will also tell us that plans to expand their research and bring more Cushing's patients into this extraordinary program have been stymied because they cannot be assured of new supplies of RU 486.

FDA officials contend that there is no link, official or otherwise, between the winding down of nonabortion research with RU 486 and the import ban.

But the reality is we are losing the chance to do cutting-edge medical research because the company that makes RU 486 is boycotting the United States for two reasons: The arbitrary, political, and unscientific RU 486 policies of the FDA, and the protests that

have been promised from antiabortion groups. The fact is the drug's manufacturer has made a business decision to use its supplies only in countries where government regulators will give them a fair shake.

The United States drug approval process, in the best of times, is a tortured exercise. At present, the FDA is underfunded, understaffed, and still reeling from the generic drug scandal. Given that RU 486 has been welcomed in other countries, it is easy to see why, from the standpoint of the company's self-interest, they have steered clear of the United States.

As a result of FDA's RU 486 policies, antiabortion politics, and the manufacturer's business decisions, Americans now suffering from horrible illnesses will not have the hope of cures they had before the import ban was imposed.

Americans with breast cancer and other dread diseases have become the innocent victims of this administration's political brinkmanship with the pro-choice movement on abortion, and there will be needless suffering.

Nonabortion research with RU 486 will be done outside the United States where the manufacturer, their licensees, and affiliated scientists have their work evaluated for its scientific merit, not its ability to meet a political litmus test.

Until the United States Government signals the world that RU 486 will be treated like any other drug, many of our citizens will have to wait to secure the multiple benefits scientists will describe today.

We appreciate the assistance of all our witnesses and the many who have helped the subcommittee during this year-long inquiry.

[Chairman Wyden's statement and staff hearing memorandum may be found in the appendix.]

Chairman WYDEN. We now call our first panel forward. Dr. William Regelson, M.D., professor of medicine, Medical College of Virginia; Dr. Kathryn Horwitz, Ph.D., professor of medicine, University of Colorado; Dr. George P. Chrousos, M.D., section chief, Pediatric Endocrinology, Developmental Endocrinology Branch, National Institute of Child Health and Human Development; Dr. Lynnette K. Nieman, M.D., Developmental Endocrinology Branch, National Institute of Child Health and Human Development.

If all of you will come forward, we have some brief formalities. We thank you for your assistance with the subcommittee's inquiry. I think the staff has advised you that it is the practice of this subcommittee to swear all witnesses who come before our subcommittee. Do any of you have any objection to being sworn as a witness today?

Please raise your right hand.

[Witnesses sworn.]

Chairman WYDEN. The subcommittee staff has also indicated we would like you to keep your prepared presentation to about 5 minutes. We have a great many witnesses, and we may otherwise be here until probably breakfast tomorrow. So, we appreciate your cooperation with a sensitivity to time.

I will make a copy of your prepared remarks a part of the hearing record in their entirety.

My suggestion is that you simply just talk to us. I know that there is sometimes an almost congenital desire to read things. But if you just talk to us, I think we will be able to get your views very well represented.

Dr. Regelson, we welcome you. We know you have done considerable work in this field. Why don't you proceed.

TESTIMONY OF WILLIAM REGELSON, M.D., PROFESSOR OF MEDICINE, MEDICAL COLLEGE OF VIRGINIA

Dr. REGELSON. It is my feeling if RU 486 were not abortifacient, it would be considered to be a major medical breakthrough. Because of its broad implications related to its effects in Cushing's disease, RU 486 is not only an antiprogestin, which makes it a contragestational agent which prevents pregnancy, but it is a corticosteroid blocking agent which blocks the action of steroids like cortisone.

For this reason, it may have implications that relate to the aging process because many of the clinical side effects we see in Cushing's disease, the thinning of bone and skin, the muscle atrophy, the development of diabetes, the deposition of abdominal fat, the suppression of immunity, all of which are seen characteristically as we grow old up into the upper years of our lives, therefore, this drug has potential beyond its implications as a population control drug, but relates to the quality of life for many of us.

More importantly, I earn my living as a medical oncologist. In 1988, I became aware of a clinical study in Montpelier, France, completed in 1987, where RU 486 was given to advanced breast cancer patients in a dose range study to determine whether or not it might have some value in breast cancer. There was significant clinical response in this population of advanced breast cancer patients.

Based upon this, we attempted to get a clinical study off the ground with the French company Roussel-Uclaf. We met with them in January 1989 and were prepared to meet with them in April 1989 to get a multicenter cooperative study going under the auspices of the National Institutes of Health with one of the major clinical cooperative groups studying breast cancer.

In addition, because this drug affects white blood cells involved in immunity, the lymphocytes in Cushing's disease, and again in animal models, we thought it might be worthwhile looking at this drug as an agent for the treatment of AIDS, and Deeda Blair of the Lasker Foundation and Baulieu, the originator of the drug to a large extent, planned to meet with Broder and the groups at the National Institute of Health involved in the AIDS program.

But in March there was a lot of agitation on the part of the right-to-lifers. In April, Roussel-Uclaf canceled all its meetings, and we were frozen out of a major clinical study in both areas.

In my own personal research work with Mohammed Kalimi, we have found RU 486 to be useful in the treatment of malignant hypertension in a rat model. Here is another potential value of this drug that requires clinical testing. The problem is an ethical issue of how does one balance, for example, the life of a fertilized egg

that has no form against the life of 43,000 women a year who die of breast cancer who conceivably could be helped by this drug.

The implications in cancer go beyond breast, because progestational receptors are present on other tumors and so are corticosteroid receptors. It may have value in certain tumors like bowel and renal cancer and other tumors. For example, it works in meningioma, which is a cancer of the covering of the brain where it produces regression.

We need to find the means of getting this drug out into the clinic for testing. I'm optimistically predicting it will be of value, but we don't know until we test. We can't test because the company has put an embargo on the drug relative to testing it in the United States and doing clinical studies.

There are many centers in this country that would be willing to work with it if there would be some support from the company guaranteeing the supply of drug and perhaps some financial support to do the work. We are stymied by this emotionalism related to fertilization.

It is my feeling that we have a problem with the FDA because they mean well, but their goal as charged by Congress is to protect our society from toxic or inactive drugs. One of the charges that Congress should give to the FDA is to make them an advocate for a crisis constituency of individuals who have lethal or severely debilitating disease. It should be the job of the FDA to expedite the entry of such drugs into this country, and they should encourage clinical trials, and clinical development, and the development of proper studies to get these drugs out.

For example, I've heard that in Stockholm they are starting a breast cancer study. Let's say they confirmed the French results and it works in breast cancer. How long will it take us in this country to have access to this drug according to the current situation as it exists? It will be another 3, 4, or 5 years. We have to change the climate.

It strikes me as being inappropriate that the climate is colored by an embargo on the part of the FDA that puts an emphasis on toxicity when that is not clearly established. It sets a tone.

I think Roussel-Uclaf is taking a political position for its own self interest, by forcing us, whether we are pro-life or profreedom of choice, to fight for the availability of this drug for that purpose. After all, abortion is a legal issue in this country. I think it is a very interesting paradox that resembles the early days of the Civil War. Suppose the State of California, if Rowe versus Wade is reversed, indicates that it wants RU 486 because it is for freedom of choice and another State is against it. Where does the Federal FDA come in? Is it the California FDA or the United States FDA that will decide? Is there any way that we could get Roussel-Uclaf to recognize the State of California as a sovereign country? Because if its attitude is one of only giving it to those countries that will accept it without political ramifications, then each State will have to make the issue on its own.

Of course, we are setting up a natural black market because one State will condemn abortion and another State will be for freedom of choice, and the drug may get loose across State boundaries.

We should be concerned with the life of those individuals who we identify are seriously up against it, as with the case of breast cancer, whose lives are limited, or the Cushing's disease patients whose quality of life is limited, or the implications that go beyond it for all of us who suffer the debility of aging, where RU 486 may play a modulating role. It is all supposition until we get the drug and try it.

[Dr. Regelson's statement may be found in the appendix.]

Chairman WYDEN. Thank you very much. It is a helpful statement. I will have questions in just a moment. Dr. Horwitz, why don't we go to you next.

TESTIMONY OF KATHRYN B. HORWITZ, PH.D., PROFESSOR OF MEDICINE, PATHOLOGY, AND MOLECULAR BIOLOGY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

Dr. HORWITZ. The reason I am here today is that I am a basic scientist, and I study the actions of sex hormones of breast cancer in a test tube.

I want to review with you the story of breast cancer in the United States. As you know, one in nine women who live to age 70 will develop breast cancer. The reason for that is not because women have breasts, as people might think. It is because they have ovaries. It is the hormones of the ovaries, called estrogen and progesterone, that lead to the development of breast cancer and that lead to the growth of breast cancer.

That is the bad news. The good news is that if estrogen and progesterone stimulate breast cancers to develop and grow, then antiestrogens and antiprogesterones should make them regress.

Antiestrogens are, therefore, a major way that breast cancer is treated in this country and antiestrogens have been available to clinicians for 20 years. However, in addition, for 20 years or more, scientists, clinicians, and patients have needed antiprogestins to take care of the other half of the story, namely, the progesterone half. We now have antiprogestins.

RU 486 is one such compound, and its rationale for use in the treatment of breast cancers is absolutely clear. As you know, initial studies in France have, in phase one trials, shown that this drug stabilizes the disease in patients in whom everything else has failed; in patients in whom antiestrogen treatments have been tried and failed; in patients in whom other types of treatments have been tried and failed; in patients in whom RU 486 was used as a last resort.

In 12 out of 22 such end-stage patients there was a stabilization or an improvement of their disease. As an interesting side effect, RU 486 also appeared to be analgesic. That is, it stopped pain due to cancer in their bones and meant that these patients could be taken off other pain killing drugs.

This drug has been found to be extremely safe. In breast cancer patients and, of course, in 50,000 women using RU 486 for other types of treatment, it has been shown to be safe. I don't believe that safety of this drug is an issue.

Antiprogestin therapy is important as a second line therapy in breast cancer. Whenever antiestrogens are used for treatment, they

eventually fail, and the next treatment is either high dose progestins or antiprogestins. So, there is clear clinical rationale for RU 486 drug in breast cancer.

But this drug has implications beyond treatment of cancers of women. As my colleague told you, there is good reason to think that meningiomas will respond to antiprogestins.

Meningiomas are very interesting brain cancers. They have high levels of progesterone receptors. Progesterone receptors are the intermediaries between the hormone progesterone, and the cell's growth regulating genes. It is the receptors that turn on genes that lead to growth regulation. It is receptors that are important in understanding how progesterone acts.

Meningiomas have high levels of progesterone receptors in men and women, and treatment with an antiprogesterone should lead to growth inhibitions of those cancers.

Clinical trials are underway in Europe to test RU 486 in meningioma. American patients who have meningioma are forced to go to Europe for treatment because they cannot obtain RU 486 in this country.

I would like to point out that beyond treatment of brain cancers or breast cancers, RU 486 has implications for treatment of many other cancers; prostate cancer as an example. Prostate cancer is another disease driven by hormones, in this case testosterone. The major way to treat it is with antitestosterone drugs.

Men don't like to be castrated, and they prefer to take an antitesterone drug. Women don't like to be castrated either, and they prefer to have an antiprogestin, rather than to be forced to undergo an oophorectomy, which is sometimes the only choice they have. We need antiprogestins, not only for cancer treatment, but to help us understand how all hormone antagonists act. There are many reasons to think RU 486 has important roles to play beyond cancer treatment. I want to list a few of them: In treatment of endometriosis; of premenstrual syndrome; to trigger labor in cases of undue delay; to facilitate postpartum milk production. These are potential uses that involve millions of women in this country.

I cannot emphasize too strongly the powerful clinical and experimental potential of antiprogestins. Scientists have sought such drugs for 20 years or more. Now that we have one, the current political climate in this country is preventing its use both clinically and experimentally.

I am a basic scientist. I study breast cancer cells in a test tube. When I put RU 486 on those cells, their growth slows down.

However, I can no longer get RU 486 for testing in a basic experimental setting. In my research, I try to understand how RU 486 stops the growth of breast cancers, how it acts on progesterone receptors, what the genes are that regulate growth of breast cancers. You need a hormone antagonist in order to understand how the hormone itself works.

It is based on the lock and key idea. The antagonist RU 486 is a lock that turns something off. It tells you exactly what the hormone progesterone is doing, and it gives you other clues about how a cancer grows and how the growth can be slowed or stopped.

The FDA's RU 486 import alert states as its rationale that the drug could pose a risk to the safety of the user. As you have heard

before, and as I am telling you again, the data do not support that contention. RU 486 is safe when used under a doctor's supervision. How the FDA arrived at its conclusion about safety is not clear.

I have called several of America's leading experts on the actions of antiprogestins in breast cancer and in reproduction to ask them whether the FDA solicited their advice about RU 486. None of these American physicians and scientists were consulted by the FDA. I have enclosed a list of these experts in the appendix of my written statement.

I believe that enforcement of the import alert means that thousands of men and women are denied access to a safe and critically important drug to treat not only cancers but to correct many other hormone deficiencies. Enforcement of this import alert means that I no longer can obtain RU 486 for basic research of progesterone receptor action in breast cancer or for study on the mechanisms of action of sex hormone antagonists.

Enforcement of the import alert is an insult to patients, their physicians, and scientists. It argues that because this drug has potential for abuse, tens of thousands of patients should be denied its legitimate use. Thank you.

[Dr. Horwitz's statement may be found in the appendix.]

Chairman WYDEN. Doctor, thank you.

Dr. Chrousos.

TESTIMONY OF GEORGE P. CHROUSOS, M.D., SENIOR INVESTIGATOR AND SECTION CHIEF, PEDIATRIC ENDOCRINOLOGY, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, NATIONAL INSTITUTES OF HEALTH

Dr. CHROUSOS. My name is Dr. George Chrousos and I'm a senior investigator and chief of the section on pediatric endocrinology in the National Institute of Child Health and Human Development at the National Institutes of Health [NIH] in Bethesda, Maryland. I am pleased to have this opportunity to tell you about my research with the drug RU 486.

I have been with the NIH staff for over 12 years, and for an equal number of years I have worked on the development of pharmacologic agents which work against the negative effects caused by too much of the natural hormones glucocorticoids. Because RU 486 does work this way, I have been conducting research with this drug for a number of years. The focus of my work has been to develop new diagnostic procedures and treatments for Cushing's syndrome, a serious, and sometimes fatal, condition caused by an excess of glucocorticoids, and to further our understanding of the role of glucocorticoids in health and disease.

RU 486, which binds to the glucocorticoid receptor and prevents the hormone from exerting its effects, provides an excellent means of accomplishing these goals.

Cortisol is a natural glucocorticoid hormone in man. Though this hormone is necessary for life, when it is secreted in excess it has profound adverse effects on the health of the afflicted individual. These effects include excessive weight gain, severe weakness, mental depression, osteoporosis—thinning of the bones—develop-

ment of diabetes mellitus, hypertension, atherosclerosis, and suppression of the immune system.

The syndrome is fatal, if left untreated. Cushing's syndrome occurs in both sexes and in children and adults alike. The majority of those afflicted with this disorder, however, are women in their third and fourth decades of life.

Spontaneous Cushing's syndrome is not a common affliction. The form of spontaneous, severe disease that we treat at the NIH affects between 250 and 1,000 new patients in the United States every year. As a result, however, of the widespread use of pharmacological doses of glucocorticoids administered for therapy of a wide range of diseases, millions of people suffer from a mild variant of this condition.

Spontaneous Cushing's syndrome is caused by tumors of the adrenal glands that secrete cortisol, or tumors that secrete another hormone called ACTH, which stimulates cortisol secretion by the adrenal glands.

ACTH can be produced either by tumors of the pituitary gland or by tumors elsewhere in other organs, such as the lungs, thymus, or the pancreas. Because these organs do not normally secrete ACTH, the Cushing's syndrome that results from such abnormal secretion of ACTH is called ectopic ACTH syndrome.

Since 1983, we have performed research at the NIH on the therapeutic use of RU 486 in a subgroup of patients with Cushing's syndrome. These patients were selected from a pool of individuals with Cushing's syndrome referred to the NIH for diagnosis and treatment. They have either the ectopic ACTH syndrome, or an adrenal tumor secreting cortisol.

Their tumor was either inoperable, because of widespread metastatic disease, or could not be located by all available diagnostic procedures at the time of initiation of therapy. All patients were gravely ill at the time that the decision was made to administer the RU 486 therapy.

The medication was given to them orally, in accordance with an NIH-approved protocol and an investigational new drug application approved by the FDA for this clinical trial. We saw positive responses in our patients approximately 2 weeks after the therapy was begun, with amelioration and gradual disappearance of Cushing's syndrome symptoms and signs.

The first patient treated with this medication was a 25-year-old man with a lung tumor which had already spread to the bone marrow. This patient, with full-blown Cushing's syndrome, due to ectopic ACTH secretion by the tumor, had a severe form of depression and had attempted suicide prior to admission at the NIH.

Before we started seeing physical changes in the condition of this patient, his mental depression was lifted in a spectacular manner with the medication. He had a 9-week course of therapy—because of limited supplies of the drug at that time—with complete reversal of the syndrome, including elimination of his diabetes mellitus and correction of his hypertension.

At the conclusion of the therapy, he underwent major surgery to remove both of his adrenal glands with no complications. Such surgery in untreated and unprepared patients with Cushing's syndrome has a very high incidence of severe morbidity or mortality.

Another patient, a 43-year-old man with an ACTH secreting tumor which could not be located, was treated with RU 486 for almost a year with excellent results. At that time, a lung tumor was diagnosed and was removed surgically. The patient's major surgery was uncomplicated and he was cured for life.

RU 486, thus, allowed both interim care until the tumor could be located, and prepared the patient's tissues to successfully withstand the necessary major surgery.

Overall, eight patients with Cushing's syndrome were treated with RU 486 for periods of 4 weeks or longer. The clinical response was excellent in five patients and the improvement was sustained for as long as treatment with this medication was continued.

Complete regression of the features of the disease was observed in all of these patients. The two patients treated for the longest periods were given the drug for 11 and 22 months, respectively.

The toxicity of the treatment with RU 486 included treatable nausea in three patients and mild enlargement of breast tissue in two male patients. Two patients developed adrenal insufficiency on RU 486, which, however, subsided with appropriate therapy.

The adrenal insufficiency was a result of administration of the drug in doses found to be too large, and decrease of the dosage was associated with elimination of this side effect.

In summary, RU 486 therapy was successful in over 50 percent of the Cushing's syndrome patients to whom it was administered. Its efficacy was 100 percent in five out of eight patients, who showed an excellent response. The side effects observed with RU 486 were mild or of a transient nature.

Appropriate individualization of the dose to achieve the optimal response to the medication, and regular monitoring of the patients on RU 486 therapy is recommended, however, because of the potential of this medication to cause adrenal insufficiency.

The patients given RU 486 should be taught to recognize the potential onset of adrenal insufficiency and how to treat themselves with glucocorticoids. A parallel situation is the self-treatment with insulin of diabetics in whom the dosage of insulin has been carefully individualized to avoid either over- or undertreatment.

According to our estimation, a small but significant number of patients with spontaneous Cushing's syndrome would benefit from RU 486 therapy each year. Mitigation of symptoms and improvement of the quality of life, as well as outright saving of life, would be expected for these patients.

In the course of our research with RU 486 and Cushing's syndrome, other important research issues involving this drug have become apparent. Given the profound roles that glucocorticoids play in development, brain function, metabolism, stress physiology, and immune system functions, the scientific questions that can be asked with RU 486, an excellent probe of glucocorticoid action, are of major importance and should be pursued.

[Dr. Chrousos' statement may be found in the appendix.]

Chairman WYDEN. Doctor, thank you very much. Your testimony is very helpful.

Dr. Nieman.

TESTIMONY OF LYNNETTE K. NIEMAN, M.D., NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, NATIONAL INSTITUTES OF HEALTH

Dr. NIEMAN. Mr. Chairman and members of the subcommittee, I am pleased to be here this morning to testify regarding research on RU 486. Since 1983, my colleagues and I have used this drug in clinical studies as members of the Developmental Endocrinology Branch of the National Institute of Child Health and Human Development at the NIH. I will review for you our published studies regarding the potential use of RU 486 as a contraceptive agent. I will also comment on the usefulness of the compound in the investigation of normal female physiology and infertility.

Because it blocks the action of the hormone progesterone, RU 486 is a compound that has great potential to aid in our understanding of normal female physiology, and to provide new approaches to a variety of conditions related to female reproduction.

To understand the excitement engendered by the recent availability of this antiprogestin compound, one must review the menstrual cycle and the role of progesterone in the reproductive function of women. The cycle begins on the first day of menstruation and leads to a pregnancy or ends on the day prior to the next menses.

During the first half of the cycle, an egg matures in one of the ovaries, surrounded by cells that make the hormone estrogen. Estrogen causes the uterus to rebuild its lining.

This half of the cycle is called the follicular phase, in reference to the maturation of the egg-containing follicle. The follicular phase ends when the fully developed egg is released from the ovary in a process called ovulation.

After ovulation, the hormone-producing cells, which previously surrounded the developing egg, form a new structure called the corpus luteum, whose function is to secrete both estrogen and progesterone. Progesterone causes the uterine lining to make and secrete new compounds and to develop further in preparation for a possible pregnancy.

After ovulation, the egg travels through the fallopian tube toward the uterus. Fertilization of the egg by a spermatozoa may occur during this journey. If this occurs, the fertilized egg attaches to the uterine lining and begins to implant around 6 to 7 days after ovulation.

If both the process of implantation and embryonic development progress normally, a hormone called human chronic gonadotropin, or hCG, is produced and reaches the maternal blood. This hormone stimulates the corpus luteum to continue making estrogen and progesterone, which are needed for the continued integrity of the endometrium. If the corpus luteum is not rescued by hCG, it stops making these steroids and disappears. As a result, the endometrium falls apart because of the loss of progesterone support, and the cycle ends as the uterine lining is shed and menses begins.

The second half of the cycle is referred to as the luteal phase, in recognition of the importance of the corpus luteum. Thus, progesterone is produced in the luteal phase, and functions to prepare the

endometrium for implantation and pregnancy, and to support the endometrium during pregnancy.

It is known that low levels of progesterone are associated with infertility and repeated miscarriage, demonstrating the importance of this hormone.

RU 486 has a structure similar to that of progesterone. Like progesterone, it interacts with the cellular machinery, called receptors, that initiate the effects of progesterone; unlike progesterone, RU 486 does not activate the receptors, and no progesterone effects result. When both RU 486 and progesterone are present, they compete with each other to interact with the receptors, and in this way RU 486 blocks the action of progesterone.

The essential role of progesterone in the preparation of the endometrium for pregnancy led us to speculate that blockade of its action would prevent the establishment of pregnancy. We have explored this hypothesis in our studies of the potential contraceptive properties of RU 486. Development of new contraceptive strategies refers to methods that would act before there is an established pregnancy.

Our studies of the contraceptive potential of RU 486 have three parts. First, we explore, in women, a physiologic effect of RU 486 that may have contraceptive properties. Second, we determine, in a laboratory animal, the contraceptive efficacy of the agent when given in a similar way. Third, we evaluate the toxicity of the agent in women and animals.

The woman who participate in our studies use nonhormonal methods of birth control during the studies and are excluded from study if they are pregnant. Thus, we have not performed a contraceptive trial of RU 486 in which the compound is given to women who may become pregnant; rather, we infer contraceptive potential from the human studies, and test it in the animal studies.

In our first study of this sort, we tested the hypothesis that administration of RU 486 in the midluteal phase would interrupt the progesterone support of the endometrium and have a contraceptive effect. Women received RU 486, at a single 10 mg/kg body weight dose, on the seventh luteal phase day. RU 486 consistently induced vaginal bleeding within 72 hours. This suggested that giving a single dose of RU 486 late in the cycle might be an effective contraceptive strategy.

To test this, female monkeys mated during each cycle were given a single dose of RU 486 or a placebo on day 25 of the menstrual cycle. None of the animals receiving RU 486 became pregnant, while the placebo-treated group had a 28-percent pregnancy rate. No untoward side effects were noted in women and no toxicity was seen in the monkeys. These data suggested that RU 486 has the potential to function as a contraceptive agent when given in this fashion.

This study represented only one of many contraceptive strategies that could be explored using RU 486. For example, we and others have shown that ovulation can be delayed or prevented completely by follicular phase administration of RU 486. The way in which the compound does this is not entirely clear.

The hormonal signal that causes ovulation is blocked by RU 486. The compound may also affect the development of the egg. These effects could be further exploited for contraceptive potential.

Since progesterone is so important during the entire luteal phase, numerous other regimens of RU 486 administration could be devised to further explore its ability to prevent pregnancy.

RU 486 is very interesting in that its effects are both dose- and time-dependent. For example, when given in the follicular phase, when no progesterone is present, RU 486 does not cause menses, regardless of the dose. When given in the luteal phase in increasing doses, menses is the first effect. At higher doses, RU 486 also decreases progesterone secretion.

Similarly, the effects on ovulation depend on the dose of RU 486 and the number of days in which it is given. Thus, one cannot refer to RU 486 as a menses inducer or ovulation blocker without stating the time of the cycle and the way in which RU 486 is given, as well as the dose administered.

One important area of inquiry in all clinical investigation is the safety of a new compound. The untoward side effects of RU 486, like its other actions, are dose dependent. We have seen no adverse effects at single doses of up to 25 milligrams per kilogram body weight, or daily doses of 3–4 mg/kg body weight given for 4 days.

One potentially life-threatening toxicity, complete blockade of cortisol action, has not been seen in normal individuals, as they respond to RU 486 by increasing the amount of ACTH, the hormone that stimulates cortisol production. In this way more cortisol is available and the RU 486-induced blockade of its action is prevented. The toxic side effects that have been observed have been seen at doses of 10 milligrams per kilogram body weight or greater, given for more than 1 week. My colleague, Dr. Chrousos, addresses this issue in his discussion of the use of RU 486 in the treatment of Cushing's syndrome.

In summary, RU 486 is a chameleon of sorts, with a variety of effects that depend on the system being examined, and the dose and frequency with which the compound is given. With regards to the reproductive system in women, there remain many physiologic questions regarding the role of progesterone that could be probed using this antiprogestin drug. The studies to date have suggested that RU 486 may have unanticipated effects, such as inhibition of follicular development, that may illuminate previously unasked questions.

Further studies of RU 486 will certainly help us to understand better the normal reproductive physiology of women. By mimicking conditions of progesterone deficiency, we hope to enhance our understanding of these conditions and expand the diagnostic and therapeutic approaches to women who are involuntarily infertile. RU 486 holds promise of providing both greater insight into infertility and new contraceptive strategies.

[Dr. Nieman's statement may be found in the appendix.]

Chairman WYDEN. Doctor, thank you. Let me thank all of you, and particularly for the manner in which you all have testified. You all are scientists. You are not politicians. It is particularly helpful for you to take us through some of the science, and also the way in which the Food and Drug Administration assessed the sci-

ence. That is one of the things I would like to focus on at this point.

Dr. Regelson, let me begin with you. You, in some of the communications you have had with our subcommittee, have raised some very serious questions about the way the Food and Drug Administration proceeded with the science in this area.

Are you satisfied that they looked, for example, at such things as toxicological data when they were considering the import ban? Do you think it would have been appropriate, for example, for them to have convened a policy review committee to assess this drug before they imposed the import ban? Do you think that they went about this matter of imposing an import ban in a scientific fashion?

Dr. REGELSON. I have no idea what occurred internally. I know Dr. Sobel is a very careful, well-organized individual who calls upon experts to advise him and does a very good job of it. So, I don't know whether he convened any group to do this.

I would say that he ordinarily, in review of preclinical material, is extremely thorough. Here, I am very doubtful that he did, otherwise he wouldn't have put the ban on.

Chairman WYDEN. Was there any effort to gather toxicological data?

Dr. REGELSON. I have no idea. I have no reference to this. I am only inferring that knowing how effective and efficient he is, I can't imagine that he did this because I don't know how he could come up with that decision if he did.

Chairman WYDEN. Do you think that should have been done in this case? That prior to proposing the import ban, there should, let's say, have been some kind of policy review committee?

Dr. REGELSON. This issue was so loaded with emotionalism that I have a feeling that the FDA was carried away by the pressures of the right-to-lifers who made this a major public issue.

You see, I don't understand it because if we are—we don't deny morphine to people who need analgesia in hospitals who are suffering pain because people on the streets are abusing narcotics. We find ways to make things available to people who have a need. There is a need out here to explore the value of this drug. What bothers me is that the FDA, by making what may be a political decision, is denying an opportunity to explore a need on the part of a large section of our population that could be conceivably helped by this drug.

The ramifications of this drug have hardly been touched upon. It releases the corticotropin-releasing factor from the hypothalamus of the brain, which is an analgesic, which has pain-relieving properties. It also mobilizes fat and causes the loss of obesity in mouse models.

Here is a drug which can possibly affect mood and could dramatically alter things like obesity, among other things. It should be looked at in these areas.

Most importantly, again, is the focus on people with serious diseases who have been denied the opportunity because of the political climate that has been set up, I think, by the FDA's decision.

Chairman WYDEN. You would be of the view that the FDA's actions with respect to RU 486 would have had a chilling effect on medical research in this country?

Dr. REGELSON. I think the problem is that we are being whiplashed here. We are whiplashed by an FDA decision which is now being used by Roussel-Uclaf who mobilized people who want the drug.

In other words, Roussel-Uclaf apparently, and I think in a sense they are unethical in doing this, what they are trying to do is whip up sentiment among those individuals who have breast cancer, who have Cushing's syndrome, and other needs for this drug to put political pressure to balance the right-to-life threatened boycott.

In other words, by doing this they are polarizing us into a position whereby those of us who want the drug for medical use are going to find it harder to get. This is designed to overcome the political agitation and threats of boycott on the part of the right-to-lifers.

Those of us, those patients and those physicians like myself who want it are being whiplashed by this fight, and we are being denied something that we all should have to explore, as part of a political maneuver.

Chairman WYDEN. One other question for you. From a scientific standpoint, is it correct to say that a variety of hormonal therapies, say, used to treat cancer, that many of those hormonal therapies would have some abortifacient properties?

Dr. REGELSON. That is a good point. Methotrexate, one of the prime drugs we saw in the treatment of clinical cancers and leukemia, is a very good abortifacient and used as such more or less illegally during the day when abortion was not a question of choice in this country.

There is another aspect to this. That is that there will be other antiprogestins that will be made available and there will be other corticosteroid-blocking agents that will be made available. Any one of these will not have been developed as abortifacient but can be used as such.

I would assume those people against RU 486 would have to agitate, and fight, and prevent us from getting these newer derivatives because they have the same abortion potential so that we will be stymied from the point of view of the development of a whole area of research because of political agitation in regard to right to life.

Chairman WYDEN. I think that is a particularly important point because what your response suggests is this is just the beginning of this fight. If there are a number of drugs now being tested or developed that could treat a wide variety of diseases but also serve as abortifacients, we will have this fight again, and again, and again, if this is not dealt with on the basis of science; will we not?

Dr. REGELSON. Yes; we will. I think an example of this is seen in Accutane, which produces fetal anomalies. Thus, if you take the drug and inadvertently get pregnant, you have to have an abortion or you may wind up with a damaged baby.

There are many people trying to stop the availability of Accutane despite the warning labels and prescription needs. Yet, what about people with pustular acne, all the adolescents whose faces are deformed, and scarred, and pitted? How does one balance their needs versus the fact that somebody doesn't read a warning label

and doesn't follow the advice in the package insert or the advice of their physicians?

In other words, I think that if we are not careful, if we don't fight this issue, I hope now, we are going to have a whole area that we will be unable to work with because of the political threat.

Chairman WYDEN. Doctor, I thank you. I would ask you more questions, but just in the interest of time I want to tell you I don't stay up nights reading medical journals under normal circumstances, but I did read your article, and I think it was very helpful. I appreciate it.

Dr. Horwitz, just a couple of questions for you. I am very troubled about the point that you made in your written statement and in your comments here this morning that the FDA didn't seem to contact any of the leading scientists in this field when it was coming to its decision with respect to the import ban.

I gather that you think that could have been appropriate and a very modest step that the agency could have taken in the name of good science. Is that correct?

Dr. HORWITZ. That goes without question. What I did was a simple thing. I said, who are my colleagues? Who are the people that I know who do research with RU 486, who know how progesterone works, who understand about progesterone receptors? Who are the major American scientists in this country who know about breast cancer? When I called them, it turned out that not one of them had been contacted by the FDA. What was most surprising to me was that not one of them knew about the FDA's import alert. I didn't know about it until your committee contacted me.

Let me point out an important problem that this import alert raises. I called the FDA regional office in Denver and asked, "Look, what does this import alert mean? I am not a Government official. I don't understand what this means. I'm just a scientist. I need to bring RU 486 into this country to study breast cancer in a test tube. Can I have it mailed to me?" The answer by the FDA was "No."

I asked, "If I have a letter from the NIH to say that I do research with RU 486, and I go to Paris for a scientific meeting, can I bring some RU 486 back with me for research?"

They told me "no." I said, "How do I get RU 486 for research?"

They said, "File an IND."

Please note that I am a basic scientist. I am not a clinician. IND's are meant for clinical research involving human use. IND's are not meant for basic research.

I said, "Please send me an IND form. I want to see what this form looks like."

As I expected, the form deals with clinical research and human subjects, which I don't do.

This means that as a result of the import alert, I cannot get RU 486 under any circumstances.

I am absolutely thwarted in getting this drug into the country for basic research, and the IND route that the FDA proposes is entirely irrelevant in my case.

Chairman WYDEN. If the manufacturer chooses to do its research in Europe or elsewhere, what are the implications in your view for the United States?

Dr. HORWITZ. I hate to brag, but American scientists are the best in the world, and American science is the best in the world. If American scientists can't do the research, then the highest-quality, best type of research will not be done.

Some research on RU 486 will be done, but we would like to see it done under the best kinds of conditions, and I think that American scientists, and especially American clinicians, need to be included in that research.

Chairman WYDEN. I just want to make sure I understood the point that you made in your oral testimony. Did you say that you were already aware of patients going to Europe for treatment in some instances? Perhaps it was cancer, I wasn't sure, brain cancer, simply because there isn't the adequate supply for the research here at this point?

Dr. HORWITZ. That is correct. American patients have to go to Europe for RU 486 treatment.

Chairman WYDEN. Dr. Horwitz, thank you. You have been very helpful, and we want to work with you in the days ahead as well.

Dr. Chrousos, let's move that microphone over to you. I want to also understand exactly what the situation is with your patients.

Are you finding that it will be difficult to get enough RU 486 to handle your existing patients in terms of the commitment you have made to them, as well as not being able to take on new patients?

Dr. CHROUSOS. Let me give you the status of all this at the present time. In 1984, we were given a supply of the drug by the company to perform a number of studies, including the one on therapy for Cushing's Syndrome.

Most of the drug has been used up, and the remaining quantity would be insufficient for continuing the therapeutic study or for initiating a new one.

Luckily, the results collected so far were adequate for proving the original hypothesis by demonstrating that the drug works, and we decided to conclude the study and submit the results for publication to a major medical journal. We would like to continue our studies with the drug in a second phase, to optimize the dosage of the medication and minimize the side effects.

However, we will not be able to initiate such a study and accept patients for treatment before we receive a definite commitment for adequate supply of the drug.

The company has refused to make such a commitment at the present time, and my colleagues and I, as well as patients who are possible candidates for treatment, are apprehensive as to whether this study, as well as other valuable studies, will be realized.

Chairman WYDEN. I just find it particularly unsettling to see that with the supply there are questions both as to whether you will have enough to meet your existing patients, and that you are not going to be able to go forward with the new research that you would like to do. I appreciate your candor in assisting the subcommittee on this.

Now, I gather that all of this has been confirmed in some correspondence with Roussel-Uclaf so that you have had discussions with them for some time, and there has also been some written correspondence?

Dr. CHROUSOS. No; we do not have a formal refusal by the company, so we don't know. They may finally make it available for treatment of patients. Simply, at this time, they wouldn't give a definite answer.

Chairman WYDEN. What reason do you have to believe that they will make it available?

Dr. CHROUSOS. Hopefully, this climate of uncertainty will end, and they will feel comfortable enough to send the drug to the United States for this kind of treatment.

Chairman WYDEN. Did they tell you that they were no longer interested in Cushing's syndrome, simply because of the political climate?

Dr. CHROUSOS. No; they never said that, although they have made public statements, which one can find in the New York Times or elsewhere, about the fact that they will not make commitments for treating these patients at the present time.

Chairman WYDEN. Your view is that the latest assessment, on the basis of your discussions with the company, is that until the climate changes, to use your words, they will make no commitments of additional RU 486 for your use.

Dr. CHROUSOS. That is what I think, but I cannot really speak for them.

Chairman WYDEN. Very good. One last question for you, Dr. Chrousos. You, as well as your associates, Dr. Regelson and Dr. Horwitz, have been working in this field for a long time. In fact, I gather that your work is some of the longest running work.

When the FDA was preparing its import ban, did they make any effort to try to reach out to you and ask your opinion with respect to the work you were doing, the safety of RU 486, to try to solicit your views prior to their imposing this ban?

Dr. CHROUSOS. No; I was not contacted, although I must mention that in our dealings with the officials of the FDA who were overseeing this trial, we have been dealt with both professionalism and empathy.

Chairman WYDEN. I appreciate that. Again, I just find it amazing to think Dr. Horwitz, yourself, people who are on the front lines of doing this work, it would have been awfully simple for FDA to get on the phone, to contact you all, and ask you about the scientific underpinnings of the work that you have been doing. Frankly, I just think it is extremely irresponsible that they didn't, and I appreciate you being clear on that.

Dr. Nieman, let me ask a question or two about your research. Some have said that RU 486 has much potential as a contraceptive and treatment for infertility.

Do you believe that there has been a reluctance to do research, not the drug's effect on the female's reproductive system, because the drug is so often perceived as an abortion-inducing agent?

Dr. NIEMAN. I can't really comment for any other individuals in the country who have attempted to obtain the drug and who might be very excited about those studies. I can say that we have been pursuing our studies at the greatest pace of which we were capable and have had no difficulty in pursuing the investigations that we wanted to do ourselves.

Chairman WYDEN. You have heard your colleagues testify today regarding problems that they have had getting the drug for medical research or problems that they anticipate that they are going to have in the future. Do you essentially share their concerns as a medical researcher?

Dr. NIEMAN. As a scientist and as a physician who treats patients, I am concerned that this research progress. It has great promise. I am not sure that any of us have adequately conveyed the excitement and the potential of this drug, and I can't comment on whether or not this drug will be available. We all hope that it will remain available and that people will be able to continue this very exciting research.

Chairman WYDEN. The committee staff has found that FDA has issued only 10 or so IND permits for investigation of RU 486, and that most of those are certainly being scaled down or abandoned.

Why has the FDA three-phase IND process had problems getting full-scale investigation and research into the possible uses, risks, and benefits of RU 486?

Dr. NIEMAN. Again, I can't comment on what has happened at other institutions. I hold both of the IND for the NIH work, and we make annual reports to the FDA each year, commenting on the toxicity of the drug, if any, and our progress with our research, and we have had no problem in continuing, and have not scaled down any of our projects, and are pursuing them.

Chairman WYDEN. OK. You have been very helpful to us today. Dr. Horwitz, would you like to add one other thing?

Dr. HORWITZ. I would like to make one other point, which is an issue that really hasn't been raised here today, and that is that this import alert has a chilling effect on RU 486 research in this country, and I would like to add that, in addition, it has had a chilling effect on the development of similar drugs by American drug companies, so that it is not just a question of importing a drug like this into the United States, but also a question of American pharmaceutical manufacturers developing similar drugs in this country.

Chairman WYDEN. I think that is an especially good point. What you are saying is that this is also going to damage American competitiveness, and the fact is, as I look around the world, the United States seems to be the only western industrialized nation that is sitting out the opportunity to be part of what researchers like yourself say is an exciting new development in the drug field. So, what we are talking about is not only holding back medical research, but also hampering our ability to compete in global markets.

Dr. HORWITZ. Exactly, and since this is a business subcommittee, you might want to take that into account.

Chairman WYDEN. You are being awfully logical, and we don't let that break into as much debate as it should here in Washington. All of you have been very helpful. We thank you, and we will be talking to you in the days ahead.

Our next panel is Wanda L. Guesnier, Lubbock, Texas; James F. Nelson, Flemington, New Jersey. We welcome you. We know you are on the front line as advocates for patients and families. We do swear all our witnesses, as you probably have gathered here today.

Do you have any objection to being sworn as a witness?

[Witnesses sworn.]

Chairman WYDEN. We are going to have to limit your testimony to 5 minutes, just in the interest of time, and we do very much appreciate your cooperation. Why don't we start with you, Ms. Guesnier.

TESTIMONY OF WANDA L. GUESNIER

Ms. GUESNIER. Thank you for inviting me here this morning to testify about my experience with Cushing's syndrome and the use of the drug RU 486.

My name is Wanda Guesnier. I am a 57-year-old secretary and mother of three from Lubbock, Texas. I am in Washington this week for treatments at the National Institutes of Health as part of my ongoing battle against Cushing's syndrome.

Cushing's syndrome is a hormonal disorder caused by prolonged exposure of the body's tissues to high levels of cortisol. It generally results from a tumor of, one, the pituitary gland; two, the adrenal glands; or, three, ectopic tumors found in any part of the body. Approximately 10 people in every million are affected by the disease.

I first became ill in December 1986. I was tired all of the time, and I experienced an unaccountable weight gain, approximately 20 pounds. At first, I attributed it to my age and continued on with my life. However, as time passed, I began experiencing symptoms that made me aware that something might be seriously wrong.

I began to experience hypertension, muscle weakness, excess hair growth, moon face, a loss of memory, extreme mood swings, and I was often disoriented. I contacted a doctor of internal medicine and underwent extensive testing. He told me that I had an extra loop in my colon and that I should go home and exercise.

By May 1987, my symptoms seemed to go into remission; the swelling went down, and I returned to normal. In January 1988, however, all of the symptoms returned. I contacted an endocrinologist who did another thorough examination. She recognized that I had the classic symptoms of Cushing's syndrome. She recognized the disease from her training at the National Institutes of Health [NIH].

I was admitted to a local hospital for an additional week of testing. I was told that normal cortisol levels run at about 90. Mine was over 9,000. My doctor immediately contacted NIH and arranged for NIH specialists to examine me as soon as possible.

Within 2 weeks, I had deteriorated to the point where I could no longer function. I felt that the end was very near. My doctor again called NIH, and I was admitted within the week.

I underwent 6 weeks of testing at NIH, beginning in February 1988. I was advised that my tumor was ectopic. Such tumors can be very small, sometimes only the size of a head of a pin, and the doctors couldn't locate my tumor. They gave me three treatment options to help lessen my symptoms. One of these options included treatment with the experimental drug RU 486. After carefully considering side effects and my prognosis, I chose to try RU 486.

A week after I first started taking the drug, the feeling came back into my arms and legs, the swelling went down, my blood pressure returned to normal, and my mind was clear. For the first

time in months, I felt like I was on the way to feeling normal again. I was released in April 1988 and returned home. At the time, I was taking 300 mg of RU 486 twice a day.

In August 1988, I returned to NIH where I underwent surgery to remove the lower lobe of my left lung where a tumor of the type that causes Cushing's syndrome had been found. Unfortunately, this did not fully clear me of the disease, and I underwent a second chest surgery in January 1989 to remove all the nodes in the areas of the original tumor, my chest and neck. In August 1989, a spot was found by MRI on the back of my left lung, and I underwent a third surgery.

At this time, Dr. Cutler, the head endocrinologist at NIH, discussed with me the possibility of removing my adrenal glands in the hope that I could return to a normal life. In preparation for this operation, my dosage of RU 486 was lowered to 200 mg twice a day with a total abstinence from the drug in the 2 weeks prior to my last surgery.

Since that time, I have been able to return to my normal life. However, they are still searching for the tumor or tumors which caused the disease and which may or may not be malignant.

I used RU 486 for 20 months with no apparent side effects. I felt extremely well during the period I used the drug and my symptoms were effectively blocked. If RU 486 can block cortisol so effectively without any side effects, surely additional research will find other equally rewarding uses for the drug. We shouldn't automatically close our minds to this drug because it can also be used as an abortifacient.

Please don't close the door to further research with this drug or close your hearts to the possibility of giving hope to thousands of Cushing's syndrome victims seeking a cure to this terrible disease.

Thank you again for the opportunity to testify this morning. I will try to answer any questions you may have.

[Mrs. Guesnier's statement may be found in the appendix.]

Chairman WYDEN. Thank you very, very much, and we will have some questions in a moment. Why don't we go in the order of the panel. Why don't we go next to you, Mr. Nelson.

TESTIMONY OF JAMES F. NELSON

Mr. NELSON. I want to thank you for this opportunity to testify before this subcommittee regarding Cushing's syndrome and the drug RU 486.

My name is James F. Nelson. I am 47 years old, married with four children, and I live in Flemington, New Jersey, where I work as a plant foreman for a plastics dispersion company.

I am here this morning to talk about my experiences with Cushing's syndrome and RU 486.

I was first diagnosed with Cushing's syndrome in 1985, December. At first I didn't think that my symptoms were all that serious. However, I soon began experiencing increasingly painful problems. My symptoms included severe mood swings, unaccountable weight gains, swollen tissue about my face and neck, hair loss, bladder difficulties, the loss of muscle, and muscular weakness.

Obviously, these physical symptoms made it difficult, if not impossible, both to do my job and to live a normal life. As the symptoms increased, more and more of my time was being taken up by medical appointments, blood tests, urine tests, CAT scans, and x rays, all looking for the source of the disease.

I began treatments for Cushing's syndrome at the National Institutes of Health in March 1986. It was at this time that I began an experimental course of treatment with the drug RU 486. Researchers had been using several other drugs to treat Cushing's syndrome, but they told me that they had very positive results with RU 486. Under the therapy program, I was taking dosages of the drug four times a day.

Within a month or two of beginning treatments with RU 486, many of the symptoms that I suffered from began to clear up. My problems with high blood pressure and hypertension lessened, my mood swings became less dramatic, and my bladder problems eased. In fact, after a few months of treatments with RU 486, all of the symptoms of Cushing's syndrome disappeared. The moon face, hair loss, swelling, the hump on the back of my neck, all went away. In short, the disease went into remission.

In all, I was treated with RU 486 for about 1 year. I feel that the treatments were very successful. I only experienced minimal side effects, such as breast enlargement. After a long, painful period where any kind of activity was difficult, I was actually able to return to some semblance of a normal life. Having gone through this experience, I feel that RU 486 made a definite difference in helping me fight this disease and in saving my life.

RU 486 gave the NIH doctors and staff the time that they needed to find the tumor that was causing my Cushing's syndrome. Eventfully, the doctors found and removed the tumor. Without RU 486, I'm not sure that I would not have been strong or healthy enough to survive that surgery.

I feel very fortunate that I was able to be part of the project testing RU 486 and that the treatment was so successful. I hope that research into the practical uses of this drug will continue, and I also hope that other Cushing's syndrome sufferers will have the same opportunities that I had.

Thank you for allowing me this chance to speak with you this morning, and I will be happy to answer any questions you might have.

[Mr. Nelson's statement may be found in the appendix.]

Chairman WYDEN. Thank you. Thank you very much, Mr. Nelson.

Ms. Hecht.

TESTIMONY OF ANDREA HECHT, PRESIDENT, NATIONAL CUSHING'S ASSOCIATION

Ms. HECHT. Good morning. I'm here today as the president of the National Cushing's Association, representing the interests of our patients, our physician experts, both endocrinologists and neurosurgeons, and the family members of those affected by this devastating and rare endocrine disorder.

The NCA is a nonprofit patient education and support organization which I started with two other Cushing's patients about 3 years ago. Our goals at that time were the same as they are today: One, to provide accurate medical information to patients and physicians regarding Cushing's disease/syndrome; two, to provide understanding and support, in any way possible, to Cushing's patients and their families; three, to help educate both the medical community and the lay public about this endocrine disorder; four, to encourage more clinical research into the origin of and the new treatments for Cushing's disease/syndrome.

At the time I helped start the NCA several years ago, I was a patient myself, recovering from a 2-week hospital stay after a pituitary surgery known as transphenoidal surgery. This surgery came more than 12 years after I was certain my Cushing's had been corrected at a major teaching hospital in southern California. Like many patients, however, I discovered that my doctors were not as informed on this rare disease as they might have been, and they also did not seek out the most current clinical treatments on my behalf. In short, they removed my healthy adrenal glands instead of my pituitary gland, in which a benign tumor was growing and continued to grow for 12 long years.

While I was recovering, I was fortunate to meet another Cushing's patient, and the initial root of the NCA began to grow. Over the past years, we have worked very hard to both reach out to patients who are suffering currently, as well as those who have suffered in the past.

There is absolutely no cure for Cushing's at this time, so patients have to learn to accept uncertainty about their medical futures, while making peace with their past. It is important for you to know that from the NCA's experience, most patients are not diagnosed correctly for about 3 years. In addition, it is not unusual for our patients to experience a 7- or 8-year delay from onset of the illness/symptoms and a correct diagnosis. Needless to say, upon appropriate treatment, patients bear a great many emotional scars throughout their recovery from Cushing's. This is not an easy disease for patients to deal with.

Let me offer you some typical remarks which we hear regularly at the NCA. This is a patient who was diagnosed 6 years ago and was ill for quite some time before a doctor recognized her symptoms:

> I saw more doctors than I can remember, was given many drugs, most of them antidepressants. The doctors were convinced that I was suffering from too much stress and, of course, hypochondria. I spent thousands on counseling which did me no good. Finally, a doctor told me that my job was probably the cause of my stress. So, I quit my job, and, of course, I lost my health insurance benefits with it. I was by that time too ill to work anyway.
>
> I was diagnosed, had a tumor removed, and was placed on replacement therapy drugs. It's been 5½ years now since my last surgery. I thought that maybe after surgery and, of course, about $30,000 in unpaid medical bills, I would be all right. If I had known what life would be like, I never would have gone through the surgery. Sometimes, I don't think I can go on like this.

As you can see, Cushing's is more than just an illness which gets diagnosed and then treated. The scars left behind from Cushing's are deep, permanent, and tender. On behalf of the more than 20,000 estimated past patients in the United States today and the

thousands more yet to come, I sit before you today to discuss the medical need for RU 486, possibly a beneficial treatment for an unknown amount of Cushing's patients.

To discuss the need for RU 486, let me first explain Cushing's to you. Cushing's is an endocrine disorder, affecting mostly women in their twenties to forties, in which the body begins to overproduce—in massive amounts—cortisol, via the adrenal glands. This process is overseen by the pituitary gland, located in between the optic nerves.

The pituitary gland in normal people sends out messages to the adrenal glands signaling when and how much cortisol is needed by the body. For example, if you have the flu, the pituitary automatically signals the need for more cortisol because of the stress the body is under in fighting the flu.

In Cushing's patients, the system still works. In fact, it over works to the detriment of the patient. The signal from the pituitary to the adrenal glands does not shut off, thus continuing to send false messages in regard to the body's need for additional cortisol. These messages from the pituitary are called receptors, and, in the case of Cushing's, the receptors are working overtime. Some of the symptoms that result because of this failed system include: Loss of menstrual periods; diabetes; high blood pressure; extreme muscle weakness; osteoporosis or brittle/broken bones; acne; facial hair growth in women; unusual weight gain, in the trunk only; easy bruising; purple stretch marks; depression; and mood swings.

Cushing's can originate in one of three locations in the body. By far, more than half of all Cushing's is pituitary in origin. Usually a very small, benign tumor known as microadenoma is discovered on the anterior pituitary gland. In some cases, a benign tumor is discovered on one of the adrenal glands. Most rare of all, is ectopic Cushing's in which a cancerous tumor, often in the lung but certainly in another part of the body, is causing the problem.

Traditional treatments to date include removal of the pituitary adenoma by a specialized neurosurgical procedure known as transphenoidal surgery, or removal of the affected adrenal gland. For many patients, these treatments relieve the predominant symptoms and reverse the process. For some, these treatments simply do not work. It is for those patients that the NCA urges you do everything you can to encourage the study of RU 486 in treating Cushing's.

As a patient advocacy organization, we believe the medical literature indicates that RU 486 presents great promise for a portion of tomorrow's Cushing's patients. There is no way for us to know how many people that might be because at the present time, there is no accurate data base from which we might extrapolate future numbers of patients.

But what we do know is this: RU 486 is a potent glucocorticoid receptor blocker. That means the drug effectively stops cortisol from acting. For Cushing's patients, this drug could prove to be one more step toward achieving a happy, healthy life once again. The NCA does not want to see the study of RU 486 blocked because politics has intertwined its issues into the progress of science. As Dr.

Richard Horton, Chief of the Division of Endocrinology and Metabolism and a national researcher and expert on Cushing's has said:

> In Cushing's syndrome, RU 486 could potentially block the action of cortisol and thus reverse and control the disease * * * I certainly favor the availability of this drug from the French manufacturer for use as an investigational tool in order to find its proper use in Cushing's syndrome.* * *

The NCA agrees with Dr. Horton's position, that RU 486 should be made available for Cushing's patients to use, when necessary.

In response to Acting FDA Commissioner James Benson's remarks that RU 486 posed unacceptable safety risks to the American public, we offer the following information: Of the thousands of Cushing's patients who the NCA has spoken to and/or heard from over the past years, every single one has supported, not only the need for effective drug therapy, even drug therapy with risks, over the option of the surgical procedure and those risks, and costs which accompany that option.

We recognize that RU 486 may not be the answer for all Cushing's patients, but for those who it will help, I can tell you, patients will be enthusiastic about its availability.

In terms of the risks associated with this drug, the NCA is presently encouraged by the preliminary studies of RU 486, which so far show the drug to be safe and effective in treating Cushing's. However, we would support large, controlled, clinical trials, managed by qualified endocrinologists who are viewed by their peers as experts in the treatment of this disease.

One of those experts, Dr. Mary Lee Vance, associate professor of medicine at the University of Virginia at Charlottesville puts it this way:

> Clinical research of RU 486 in the United States has been very limited and this needs to be changed. The endocrinology community would welcome this opportunity to study this drug in detail to determine its efficacy and safety. This is only possible if the drug is made available to the appropriate investigators, and I fully support any efforts to permit these needed studies.

In terms of the controlled use of RU 486 in Cushing's studies, and possibly eventual expanded treatment, the NCA anticipates that the drug would only be available through a highly trained physician. This is not a drug that can or should be used without strict medical supervision, much like other treatments for Cushing's. We see the availability of RU 486 as a long-term benefit to Cushing's patients who need it, and we also see this drug as posing no public health problems in the United States.

In support of these views, we are including a sampling of letters from some of the 44 physician experts who are on the NCA's physician referral list. These endocrinologists are enthusiastic about the future clinical trials and possible availability of this drug for their patients in the future. The NCA is enthusiastic, too, because we hope that RU 486 will soon be another medical option in the list of treatments used to combat this devastating endocrine disorder.

Thank you for asking us here today, and we thank you for your time and attention.

[Ms. Hecht's statement, with attachment, may be found in the appendix.]

Chairman WYDEN. Thank you for your very helpful testimony. Let me say at this point that I am going to have to keep everybody

to 5 minutes, otherwise, we will be here forever. Frankly, I would like to listen to all of you for a lot more than 5 minutes, but I don't think we can get our room for that much longer. So, let's go forward with that kind of cautionary comment.

Ms. Zakarian, we welcome you as well, and please proceed.

TESTIMONY OF BEVERLY ZAKARIAN, PRESIDENT, CANCER PATIENTS ACTION ALLIANCE

Ms. ZAKARIAN. I am going to excerpt my comments, so you can expect some ums and hums.

I want to thank you for inviting me to appear here to explain my experience and how it relates to RU 486.

In 1985, I was one of 18,500 women diagnosed with ovarian cancer. Thanks to medical and scientific advances in the treatment of this disease, I'm one of the only 7,200 who is still alive 5 years later. I have survived, but it's changed my life, because I have devoted the rest of my life to helping others have the same opportunity for treatment as I myself had.

I had stage III ovarian cancer, which is the stage at which most ovarian cancers are diagnosed. That is, there is some spread into the pelvis and abdomen. My prognosis was guarded. This is a hidden disease, and a very dangerous one.

I had chemotherapy, one treatment of high dose cis-platinum. Before 1979, there was no effective treatment for ovarian cancer. A fortuitous discovery by a researcher led to the advance of the platinum treatment. Prior to that, a good response to treatment for ovarian cancer was 3 to 6 months life extension. But platinum had several drawbacks. It was very toxic to the kidneys and to nerve endings, and a patient had to be hydrated in hospital to get the drug in and get it out.

I began to experience, after the one treatment, very toxic side effects. I had hearing problems, because, indeed, deafness is an expected side effect of treatment with cis-platinum.

I had numbness in my fingers, and, indeed, my right index finger became paralyzed. I'm an artist, and my right index finger, of course, is very important for fine motor control. This kind of nerve damage is also an expected side effect. In fact, Gilda Radner, who died of ovarian cancer, wrote very movingly about the fact that she had difficulty writing her book because of numbness in her fingers.

Quite by chance, I had read in the Times a report of a new drug, an analog of cis-platinum, that was starting clinical trials, wide-scale trials in 1985. That drug had been developed by the same researcher, an American scientist who had developed cis-platinum. It was, however, just leaving small scale trials after several years, and starting wide-scale human trials here. It was in wide use in other medically-advanced countries of the world. It was the standard drug for treatment of ovarian cancer.

I managed to get it on a compassion release basis, because I had been already showing such toxicity as a result of the cis-platinum. The choice that I had to make, of course, prior to that was a future, perhaps deaf, perhaps paralyzed, perhaps on dialysis, or no future at all, and this is a choice that no patient should have to make.

It's imperative that there be as many therapeutic drugs available to cancer patients as there are drugs effective against cancer. People can become resistant to drugs after extensive use.

Combination chemotherapy demands by definition that different drugs be available and used, because the drugs attack the tumor in different stages of growth, and by different means. Since some cancer drugs are themselves carcinogens and cause secondary cancers, there is a time limit on the usefulness of certain drugs. Indeed, every cancer case is an individual one, and every patient must be treated with the drug to which they respond.

Thanks to my treatment with the then new cancer drug, which only now, 5 years later, is approved by the FDA as a second-line treatment for ovarian cancer, I'm able to sit before you here and speak for your constituents and mine.

I'm the president of Cancer Patients Action Alliance, and we are committed to getting drugs out of the FDA and into the bodies of patients who need them to save their lives.

Cancer Patients are a right-to-life group, too, and RU 486, which may save lives, is needed by cancer patients and other patients. Any drug that shows promise must be investigated. Research must absolutely not be hindered by political and narrow religious interests. There are 1 million new cancer patients a year. Cancer does not strike along political or religious lines. Democrats and Republicans, conservatives, too, Protestants, Jews, Muslims, and all the ethnic groups that make up our diverse American population, all want to survive cancer, and it's up to you and us to help them do it. Thank you.

[Ms. Zakarian's statement may be found in the appendix.]

Chairman WYDEN. Thank you. Very well said, and within 5 minutes, too.

Helen Byrne, vice president, Cancer Patients Action Alliance, New York. Ms. Byrne.

TESTIMONY OF HELEN BYRNE, VICE PRESIDENT, CANCER PATIENTS ACTION ALLIANCE

Ms. BYRNE. I will reduce the amount of my talk, and hopefully I'll make it within 5 minutes. I had, in 1982, a bout with breast cancer. I had surgery, and the surgery was for a bilateral mastectomy, which resulted in the removal of 38 lymph nodes—18 of them showed metastatic tumors. In other words, I had stage III breast cancer.

Right after the surgery, I remained in the hospital and started chemotherapy. My chemotherapy consisted of methotrexate, fluorourcil, cytoxin and Adriamycin, with testosterone intramuscularly. Shortly after I began the chemotherapy, all my hair fell out, and that was just another blow. It was very devastating. I really, at this point, didn't want to live.

But I went back to work in about 5 weeks after my surgery. I still had a lot of bandages and a lot of stitches in me. But I continued my chemotherapy for a year and a half. I'm still now taking tamoxifen twice a day, and I'll probably take that for the rest of my life.

The reason I'm here today is because of RU 486, which is a possible treatment of breast cancer. But this drug requires research and testing before it can be administered. However, there is a question of whether or not the drug should be even tested because one effect is it may cause abortions. Once this effect was discovered, the pro-choice lobbying wanted testing to begin in the United States. Some testing has been done in Europe. The pro-choice lobby seized RU 486 as the answer to their dilemma, but the pro-life lobby wants testing banned because it will take the lives of the unborn. Both groups are involved in lobbying because they see the issue as abortion. Both groups have put aside as secondary, the women's issue, breast cancers.

I'm a practicing Catholic who's unalterably opposed to abortion. The issue here is not abortion. The issue is the life or death of women with breast cancer. Without testing, we will never know if RU 486 is the solution to breast cancer. We must not continue to allow women to die unnecessarily because of a variety of agendas.

There is a major moral agenda here. Should we turn our backs on women and let them continue to suffer and die because we stop research?

The argument about an evil effect doesn't work. Many prescribed and over-the-counter drugs are taken for purposes other than those intended, such as sleeping pills, diet pills, cough medicine, rubbing alcohol, and even hair spray.

RU 486, if tested and approved, would be prescribed by physicians for breast cancer. I'm not a theologian, but I do know that in theology there is a theory of double affect. That states we must look to the greater good, even if some evil happens. If RU 486 is tested and approved and saves the lives of women, many of whom have had and are raising children, then that is the greater good.

The purpose of CANACT is to bring to the attention of the American public the need to move forward on drug testing for cancer prevention or cure. Why is it possible for Europe and Canada to have drugs for cancer prevention, cure tested, approved, and on the market years before these same drugs are tested, and approved, and available to the American public?

This delay is causing the deaths of thousands of Americans who can't afford to go to Europe or Canada for treatment. The physician and oncologist is the expert. When drugs are tested and approved, a decision on combination use should be left to them and the patient. Cancer patients should not have to be patient. We should not have to die quietly while the bureaucracy drags its feet, and groups with other agendas divert the real focus, the prevention and cure of cancer.

Thank you for inviting me here today to address the committee on behalf of CANACT and as a breast cancer survivor.

My experience is not unique. I was lucky. The chemotherapy I was given saved my life. Not everyone who takes chemotherapy has the same reaction to similar drugs. Others may not have been able to tolerate the combinations of drugs that were given even to me. What works for one does not work for all. We recognize the need for careful testing of drugs before they are approved, but we are at war. We have 150,000 casualties every year and 44,000 fatalities from breast cancer alone. These numbers are on the rise.

There is no excuse for not testing and exploring every avenue until such time as women no longer have to live in fear of breast cancer. Thank you.

[Ms. Byrne's statement may be found in the appendix.]

Chairman WYDEN. Thank you. You are so right to say that this is a war. I think that just sums it up real well. We will have some questions in a moment.

Dr. Allukian.

TESTIMONY OF MYRON ALLUKIAN, JR., DDS, MPH, IMMEDIATE PAST PRESIDENT, AMERICAN PUBLIC HEALTH ASSOCIATION

Dr. ALLUKIAN. Good morning, Congressman Wyden. Thank you for this opportunity to speak to your subcommittee.

My name is Myron Allukian. I'm here today on behalf of the American Public Health Association. I'm the immediate past president of APHA, and I was also a member of the scientific delegation that visited the manufacturers of RU 486 this summer.

APHA is the oldest and largest public health association in the world with a collective membership of over 52,000 health professionals representing some 77 different health disciplines.

Our association is also the secretariat for the World Federation of Public Health Associations. Our primary purpose is to promote and protect the health of the American people. Our association is deeply concerned about the health status of all Americans, and about the cost, quality, and access to health services for all segments of our population.

As you know, our country is currently spending over $660 billion a year for health services, more than any other Nation in the world. Yet, in spite of those expenditures, we are slipping in our health status internationally. We have dropped from fifth to twenty-second in our infant mortality standing.

There are many reasons for the slippage. One of the major reasons is bureaucratic or political barriers. Today's hearing is about a political and bureaucratic barrier.

I believe that the import alert that the FDA has taken will have a negative effect on the health of the people in our country, and is not in their best interest. It also has a negative effect on cost, quality, and access to health services. Our country should use every opportunity to research, develop, and implement new and better ways to prevent and treat disease.

RU 486 has enormous potential in this area, and RU 486 should be given every opportunity to be tested, developed, and utilized. The FDA position demonstrates a profound ignorance to the potential of RU 486 and how it may benefit the American people. RU 486 and the FDA import alert sends the wrong message to researchers, academics, health professionals, and the public at large.

This summer, as part of the delegation that met with the president of Roussel-Uclaf and the health policy leadership of Hoechst, the parent company, I was very impressed with their high ideals and concerns about public health and safety. Some 50,000 women in France have successfully used RU 486, yet it's not available in our country. It's a safe, economical medical alternative to a surgical procedure. It's easy to administer, does not need anesthesia,

and allows women more privacy and control over their personal health services.

We also met with the Minister of Health's staff and learned that in obtaining RU 486 for the people of France, the Minister of Health at that time said that RU 486 is the moral property of women.

You have heard testimony today about other potential benefits of RU 486. For example, endometriosis, which affects 5½ million women in Canada and the United States, a variety of cancers, some 1 in 10 women in our country will have breast cancer, and even meningiomas, and viral infections. RU 486 also has some potential to help with HIV infection or AIDS.

The research community must be allowed to do the research, otherwise, we will not find better ways of dealing with these diseases. Politics and the outcry of a vocal minority should not interfere with medical research that has potential to improve the quality of life of millions of Americans.

The fact that RU 486 is an effective abortifacient should not be a factor in the FDA's decisions. Unwanted pregnancies in our society continue to be a serious problem, and regardless of one's moral perspective, the facts are disturbing. Over 56 percent of the 6 million pregnancies in our country are unintended. Among single teenagers who become pregnant, 92 percent are unintended. More than 1 million teenage girls in the United States become pregnant a year, of which over 40 percent have abortions. Sixty-seven percent of teen mothers and their children live in poverty, and only 1 in 50 will finish college.

When you see how our teenage girls under age 15 are doing relative to their counterparts in other countries, they are five times more likely to give birth than their peers.

Regardless of one's moral and religious beliefs, the facts vividly portray the lack of society's commitment to our Nation's youth, the indigent, and women. Our Government agencies must be credible and responsible in their decisionmaking which should be based on scientific facts, not emotions.

As the father of 6 children, ages 4 to 13, I want to be sure that my children have the best that our society has to offer. As a public health professional, we must continue to find ways to improve the quality of life for all Americans.

I urge you and the members of your committee to do everything in your power to make RU 486 available in the United States. Thank you.

[Dr. Allukian's statement, with attachment, may be found in the appendix.]

Chairman WYDEN. Thank you very much, Dr. Allukian.

Dr. Seward, we welcome you.

TESTIMONY OF P. JOHN SEWARD, M.D., MEMBER, BOARD OF TRUSTEES, AMERICAN MEDICAL ASSOCIATION

Dr. SEWARD. Thank you, Mr. Chairman. My name is P. John Seward. I'm a physician in family practice in Rockford, Illinois. I'm also a member of the board of trustees of the American Medical Association.

The association appreciates this opportunity to appear before you today to discuss the availability of RU 486. The AMA supports the legal availability of RU 486 for appropriate research and indicated clinical practices. This position derives from our very real concern that politics or ideology could interfere with well-established legal decisionmaking processes for approving the use of drugs in the United States, which is and must always be based on good science and proper medical practices, nothing more.

As we understand the current situation, limited research is going forward on RU 486. Therefore, to our knowledge, no new investigation or new drug applications either are pending or have been recently approved by the FDA for RU 486. However, if this drug can be shown to be safe and effective medical treatment, it should be available for the appropriate care and treatment of patients. There are studies that indicate, and you have heard these today, RU 486 may be effective treatment for other diseases—treatment of breast cancer, endometriosis, Cushing's disease, and hypertension.

Testing for these diseases has not been completed using RU 486. The only way to make these determinations is to conduct the necessary research in clinical trials required by law.

For the same reasons drugs proven to be safe and effective should not be kept out of the United States for clinical reasons, so also should the high standards we have for approving drugs not be contravened for political purposes.

Apparently, what has obstructed research in RU 486 is the manufacturer's unwillingness to make the drug available in the United States over the concern over the political controversy that has followed this drug. While the French Government compelled the French manufacturer to make the drug available in that country, we do not believe this is a problem that can be easily addressed under the current law.

Under the current system, which is the world's standard for the development of drugs, the manufacturer is well within its right to hold the drug from distribution. In general, the AMA stands by the FDA's appropriate application of its legal responsibility for protecting the health and well-being of the people from unsafe drugs. At the same time, though, we would expect that, if an acceptable IND for RU 486 is submitted, the FDA would approve the IND as importation would be allowed.

We hope that RU 486 can be made available and adequate research eventually can be conducted in this country to determine the drug's safety and its effectiveness for its known uses and other uses that may well be appropriate.

If I can digress, Mr. Chairman, as a family physician, I greatly respect my research colleagues, who you have heard previously, and require them to come up with new tools for me as a family physician to use. When my patients come in, their cancers are not in a petri dish. The concern is in my patient. When someone with meningioma comes in, it is a patient I have known for 20 years. I know to hold their hand because I know it is inoperable.

What we are really talking about here, what we need to be able to say, and what the American Medical Association is saying, is that we are committed to assuring that patients have every opportunity to receive the best possible medical treatment.

When potential research into drug therapies does not occur, for whatever reason, the likelihood that the best care will not some day be available is greatly increased. This is the American Medical Association's greatest concern on this issue, Mr. Chairman, and we thank you for your attention.

[Dr. Seward's statement may be found in the appendix.]

Chairman WYDEN. Doctor, thank you. It seems your testimony is a good way to wrap up. As I understand it, the AMA is saying, treat this drug like any other drug. If it meets the regulatory requirements laid out in our statutes, it ought to be approved. If it doesn't, it shouldn't be approved. Politics ought to be put aside.

Dr. SEWARD. You have articulated it very well, Mr. Chairman.

Chairman WYDEN. Just a couple of questions for you. You all were so good and laid out the issues very succinctly.

Ms. Hecht, listening to the NIH witnesses in particular, aren't you all a little bit more worried now about the future of the Cushing's research and the ability of your people and others who work with you to be part of these clinical trials?

Ms. HECHT. I am very concerned. I am very concerned for the patients who are going to have to go through the pain and agony of waiting all those years to first get diagnosed and then potentially to be denied the opportunity to be treated with something that might hold the promise for success. That is sort of a double whammy. I don't think that is very fair.

Chairman WYDEN. Ms. Zakarian.

Ms. ZAKARIAN. I am not as concerned. Of course I was horrified to hear the specific testimony. But I think that it is very, very clear that this is simply a political issue.

I think the point is that we have to get out there and raise the level of consciousness of this issue. The abortion, the pro-choice decision in this country is overwhelming. If those people understood the implications of this too, once we get them behind us, I think that the decision will follow the legal pro-choice.

Chairman WYDEN. Ms. Byrne, your testimony is very powerful. I would really commend it to anybody who is following this issue and studying it because it seems to me that you lay out what the stakes are all about.

Ultimately, this has got to be about medical research that is a lifeline for millions of people. No matter where you stand on the abortion issue, there simply can no longer be Government actions that derail access to this research. Is that essentially it?

Ms. BYRNE. Absolutely; before I came here, when I was asked if I would come down, I really had to think very seriously about this issue because I am opposed to abortion. It didn't take too long to figure out that the issue is not abortion; the issue is cancer, and we can't wait.

I can't understand why this country is lagging behind Europe. We shouldn't be. So, yes.

Chairman WYDEN. My sense is, and we got into this a little bit with Dr. Regelson, that this is just the beginning of this debate. This is going to happen again, and again, and again because many of these drugs will have multiple benefits. They will be able to address cancers and possibly be used as abortifacients.

What you are saying is, draw the line here. Say that this is a matter of life and death to people who depend on the research, who come down in favor of life, which means that this medical research gets done.

Ms. BYRNE. Absolutely; I certainly think that the pro-life people should be aware of that. If they are concerned about abortion, they should be concerned about life.

Chairman WYDEN. Dr. Allukian, you are familiar with how the drug is used. Could you describe for us some of the circumstances under which the drug is administered, and particularly what you know about the controls that are placed on it?

Dr. ALLUKIAN. In France, where it is used predominantly, it is very well controlled. There are only certain hospitals that utilize the drug. There is data collection on every patient who uses the drug.

I think one of the reasons that they are so cautious is that they are concerned about being used politically by, say, pro-lifers or by individuals who want to sue the company saying that there are negative effects when there are none. I think that is the primary purpose the company is so insistent in terms of the data collection and the control of how their drug is utilized.

I would also like to say that when we met with the president of Roussel-Uclaf and their medical director, I was part of a delegation of scientists and feminists. We presented them with some 115,000 signatures of individuals who had signed petitions for RU 486 to be made available in the United States.

They were somewhat surprised that there were people in this country who were interested in having RU 486 in the country because they had not had any requests from any official agencies or national organizations for the drug. They did make it a point to say, we like to be invited or asked to come in.

I also have with me petitions signed by some 1,000 scientists and health professionals, many of them very distinguished, representing all spectrums of health and public health, who would like to see RU 486 in the United States.

Chairman WYDEN. The APHA statement is exceptionally strong. I serve on the Health Subcommittee, and I have read your testimony and that of members of your organizations for many years. It seems to me this is some of the strongest I have heard.

What you are saying is FDA's approach on RU 486, in effect, could lead to a type of scientific censorship in this country where you simply don't have the opportunity for research and discussion about the drugs that have an abortifacient aspect. Is that what the concern is about this issue with APHA?

Dr. ALLUKIAN. Absolutely. The decisionmaking of the FDA should not be based on who yells and screams the loudest, or who is most influential, or who is in the White House at the time, or who is being influenced by who. The FDA should be making their decisions based on scientific fact, pure and simple.

If you allow the FDA to become politicized as it seems to be in this case, then their credibility and the credibility of our Government and country suffers dramatically, and the American people will end up suffering.

Chairman WYDEN. One question for you, Ms. Guesnier, and we appreciate your organization and all the advocacy that you all have done.

As we understand your testimony, prior to the clinical trials using RU 486 that you were part of and also, I gather, some of your members, there was little that doctors were able to do that really helped to alleviate symptoms of pain and discomfort that you had; is that correct?

Ms. GUESNIER. Yes; many of the doctors do not recognize Cushing's syndrome. They look at the symptoms and apply it to some other disease, or not knowing, they give you what they think may help at the time. This is one of the big problems for many of these people who go for years without their disease being recognized. They do not recognize it on the outside.

Chairman WYDEN. Mr. Nelson, is that a fair assessment of your situation as well?

Mr. NELSON. No; I was very fortunate to get referred to a doctor, an endocrinologist, who did a study at NIH. He recognized the symptoms right away, and he was looking for it.

Chairman WYDEN. RU 486 did help you significantly?

Mr. NELSON. Yes; the RU 486 took me back to normal up right until I had my surgery. With the RU 486, right after my surgery, my cortisone levels went back to normal. I didn't have to do any further medication like a lot of the patients had to. It was probably due to the RU 486.

Chairman WYDEN. You all have been very helpful. Do any of you wish to add anything further, or we will excuse you at this time.

Ms. ZAKARIAN. I would like to thank you for all of those of us who have been affected by various diseases for having these hearings which are so important.

Chairman WYDEN. You are kind. I don't want to turn this into a bouquet-tossing contest, but we appreciate what you are doing, and we will be working with you in the days ahead.

We are going to take a 5-minute break. It is literally going to be a 5-minute break, and then reconvene for our third panel.

[Recess.]

Chairman WYDEN. The subcommittee will come back to order. We thank you for your patience. It has been a long morning.

For the record, Ronald G. Chesemore, Associate Commissioner, Regulatory Affairs, U.S. Food and Drug Administration in Rockville; Dr. Solomon Sobel, M.D., Director of Division of Metabolism and Endocrine Drug Products at the Food and Drug Administration in Rockville; and Sandra Barnes, Office of the General Counsel, U.S. Food and Drug Administration in Rockville, Maryland are with us today.

I think you all are aware of our rules with respect to appearing before the subcommittee. Mr. Chesemore, I gather that you will be making the only prepared statement for the agency, but your associates might respond to some of the questions?

Mr. CHESEMORE. Indeed, I hope so, sir.

Chairman WYDEN. That is your preference? All right. Why don't we swear all of you in at this point.

[Witnesses sworn.]

Chairman WYDEN. We will make your prepared testimony a part of the hearing record in its entirety, Mr. Chesemore. Why don't you just proceed in a way that you think adequately addresses the views of the agency on this issue.

TESTIMONY OF RONALD CHESEMORE, ASSOCIATE COMMISSIONER, REGULATORY AFFAIRS, U.S. FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY SOLOMON SOBEL, M.D., DIRECTOR, DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS, AND SANDRA BARNES, OFFICE OF GENERAL COUNSEL

Mr. CHESEMORE. Thank you. I will summarize some of the opening statements in our testimony. Then we will respond to questions.

We are pleased to be here to discuss the FDA's activities with respect to the unapproved new drug RU 486. As you have heard this morning, the drug is approved in France for early abortion through a limited distribution system when used with one or two prostaglandins also approved in France. This drug is the subject of an import alert, which means, if observed coming into this country either in the mail or on someone's person, it is subject to detention by officials of the Food and Drug Administration and the U.S. Customs Service.

I should make the distinction, however, that with respect to the importation of unapproved drugs, those drugs under an investigational new drug application can be imported for research purposes. However, individuals cannot import an unapproved drug for personal use unless it meets certain criteria. In the case of RU 486, importation for research for any therapeutic use could occur if an approved IND exists.

Strictly interpreted, the Federal Food, Drug, and Cosmetic Act prohibits the importation of any drug that is not approved in this country. However, FDA, for many years, has exercised its enforcement discretion to allow the importation of small amounts of drugs for the personal use of patients provided they do not pose unreasonable or significant safety risk and provided they meet other criteria.

If I might, Mr. Chairman, I would like to submit for the record FDA's pilot guidance regarding this policy and also our regulatory procedures guidance regarding personal importation for our manual.

Chairman WYDEN. Without objection, those will be entered into the record.

[The information may be found in the appendix.]

Mr. CHESEMORE. What are these criteria whereby we might allow importation of unapproved products? One is that certainly it has to be for the individual patient and has to be of a small quantity, which we usually say is a 3-month supply or less.

The product is intended to treat a condition of serious nature, and there is no other treatment commercially available in this country. There is no known promotion or commercialization of the product. The product does not pose unreasonable safety risk to the patient. The patient confirms that the product is for his or her per-

sonal use and provides the name and address of a practicing physician who will be responsible for his or her treatment.

These criteria are considered on a case-by-case basis. In those instances where the agency determines that these criteria are not met, the agency may issue an import alert.

With respect to human drugs, the agency has some 55 to 60 import alerts in effect, one of which deals with RU 486 as an abortifacient.

The FDA does not conduct research on new drugs introduced. Those are to be conducted by the drug sponsor. But it is the obligation of the Food and Drug Administration to review the safety and effectiveness of clinical trials.

Since neither RU 486 nor either of the two prostaglandins in France were approved in this country, FDA has not evaluated their safety and effectiveness, nor have we evaluated what controls might be appropriate in this country to insure their safe use.

Although FDA can regulate the conditions of use for investigational drugs covered by an IND, no such controls can be in place to insure safe use of the products if they were imported by an individual for personal use.

We, therefore, did become concerned that the publicity regarding the availability of these drugs overseas might create a demand in this country which could in turn foster importation of these unapproved drugs leading to unsupervised and/or perhaps clandestine distribution.

We also took an action to issue the import alert because, as an abortifacient, RU 486 is not proposed for treatment of a condition for which no alternative treatment exists.

In addition, the agency could not conclude that RU 486 and the prostaglandins as they might be used as an abortifacient pose no significant health risk. The agency was concerned that because of the intended use of RU 486, potential users might well not be under the care of a physician.

We did issue the import alert on June 9, 1989, and I would like to submit a copy of that for the record also, Mr. Chairman.

Chairman WYDEN. Without objection, so ordered.

[The information may be found in the appendix.]

Mr. CHESEMORE. We are aware of AMA's resolution adopted at its June 1990 meeting supporting, and I quote, "the legal availability of RU 486 for appropriate research and, if indicated, clinical practice."

We are certainly in agreement with that resolution. We have a process whereby clinical research can be undertaken in this country and where RU 486 could proceed. It is the opinion of the Food and Drug Administration that we place no barriers in the way of research, and we could supply ample documentation of this fact to the committee in executive session, if it so desires.

It is incumbent upon a sponsor to initiate the request to begin studies by submitting an application to the FDA. The FDA is committed to maintaining the scientific integrity of our new drug testing and approval process carried out under the existing laws enacted by Congress.

Thank you, Mr. Chairman. I would be pleased to respond to any questions.

[Mr. Chesemore's statement, with attachments, may be found in the appendix.]

Chairman WYDEN. Thank you very much, Mr. Chesemore. Let me ask you a few questions to begin. Then I want to ask you about some of the documents in FDA's file on this as well.

At the time of the issuance of the import alert, did the FDA have any evidence that a black market was developing on RU 486 in the United States?

Mr. CHESEMORE. I do not believe we had any concrete evidence. We were concerned that possibility could exist.

Chairman WYDEN. At the time of the import alert, did the FDA have any evidence of surreptitious entry of RU 486 in the United States?

Mr. CHESEMORE. We did not.

Chairman WYDEN. At the time of the import alert, did the FDA have any evidence that would indicate that the drug would not be used under the tightly controlled circumstances that the company imposes for use of the drug?

I want to just make sure we are talking about the same thing. To get this drug, you have to take it at a clinic, return a few days later for the secondary treatment, the prostaglandin treatment. People can't just walk out of these clinics as if they were taking a bottle of aspirin. They are not putting it in their pocket, and jumping on a plane heading to New York City, and bringing it into the United States.

Did the agency have any evidence at the time it issued the import alert that this drug would be used outside those tightly controlled circumstances that I described?

Mr. CHESEMORE. I think the agency indeed was concerned that the drug would not be supervised because of the indications for the use. As I said, we had not looked at the safety and efficacy of the product. The application for this had not been received by the agency. We were indeed concerned that the drug would not be used under supervision.

Chairman WYDEN. You were concerned. But at the time of the alert, you didn't have any evidence, any evidence from anywhere else, for example, any other country, that the drug was being used outside the tightly controlled circumstances; isn't that correct?

Mr. CHESEMORE. That is correct.

Chairman WYDEN. OK. Now, the scientists that we had today have been working in the field for quite some time and were very critical that the agency didn't contact them with respect to their views about their work and how that might have factored into the agency's decision. Dr. Horwitz, in particular, appended to her testimony a list of scientists who had been leaders in the field, none of whom were contacted.

Why didn't the FDA contact any of the leading scientists in the field to solicit their views with respect to health risks associated with their work prior to issuing this import ban?

Mr. CHESEMORE. As you know, Mr. Chairman, there are many decisions made by the agency where we do not contact people outside the agency prior to making that decision. We were certainly aware of the research under approved IND's that was going on in this country. We were aware of the potential benefits of this drug for

purposes other than the abortion use. I might ask if Dr. Sobel would like to add anything to that response.

Chairman WYDEN. I am happy to hear from you, Dr. Sobel. I want to again see if I can understand why the agency, given the controversy associated with this drug, wouldn't contact the leading scientists in the field to get their assessment. Some of these scientists are on the Government's payroll, and they weren't contacted. Why not?

Mr. CHESEMORE. There was no intention of this import alert having any effect on legitimate IND use of the product in this country. The alert was to try to protect individual citizens in this country.

Chairman WYDEN. The point is the import ban was issued on the grounds that the drug was a health hazard. Specifically, we have cited the words the agency said it could be a threat to the safety of the user. Why didn't you contact any of the scientists who could have told the agency about any possible risks to users?

Mr. CHESEMORE. I, again, would defer to Dr. Sobel. I just think that the agency probably knew without contacting these individuals some of the potential risks and benefits with respect to this product.

Dr. Sobel.

Chairman WYDEN. Doctor, did you want to add anything?

Dr. SOBEL. I think that the main thing to do now, so we don't cross over lines too freely, is to realize that there are two different universes in the use of this drug. The safety issues that apply to the area that we are concerned with on the import alert has nothing to do with the safety issues that apply to the other researchers.

In regard to pregnancy, the safety issues involve primarily bleeding complications after the uterus is emptied. This has no relevance to the other areas of research.

I would say this. We fully support through our process and have been very cooperative with the IND holders. I would be very unhappy to see research in any way interfered with.

On the other hand, the regulatory decision of an import alert in regard to pregnancy is an entirely different universe, and I think that has to be understood.

Chairman WYDEN. Any way you slice it, the scientists now say this drug has multiple benefits. Those who are doing some of the cutting-edge research weren't contacted. Did you contact the researchers at the USC who were doing research with RU 486 and abortifacient?

Dr. SOBEL. We would in no way interfere with their research. If that should occur, I wish they would contact the division directly. I think what we are seeing here is crossing of lines both in the contribution to the situation of the FDA and the contribution of Roussel-Uclaf. I don't think we should cross those lines too freely.

Chairman WYDEN. It is a fact, however, that even if you accept the view that this drug with multiple benefits does cross some lines, you have not, nor Mr. Chesemore, confirmed that you even contacted any of the scientists who are doing work with RU 486 as an abortifacient before this drug was declared a health hazard.

Dr. SOBEL. Let me say, and I can reveal this because the publications have come—ordinarily we can't reveal the existence of an

IND—we have been following the research of the Population Council in New York, who, working with Dr. Daniel Mishell on the west coast, has done very nice research in this arena.

We have reviewed the toxicology prior to permitting that IND to develop. To say we have not been following the research or not contacted a scientist again crosses lines which should not be crossed.

We have constant review of the research in that area. I don't believe it is proper to say that there has been a communication barrier in regard to Dr. Horwitz's research. I feel bad that she thinks she is going to have a problem. All she has to do is call our division, and we will make sure there is no block on the importation of the drug she needs for her research. Let's keep the areas clearly separate.

Chairman WYDEN. Now that we have established no scientists were talked to, let me ask what scientists——

Dr. SOBEL. We haven't established that.

Chairman WYDEN. You told me in answer——

Dr. SOBEL. We have a full file of ongoing communication with scientists.

Chairman WYDEN. In addition to your telling me that you did not contact USC, where there was specific research being done on RU 486 as an abortifacient, you said you relied on studies. We cannot find in the files any evidence of which particular studies were relied on or what specific work you are talking about. Can you point to something in the files which would be a study that you felt was so persuasive that this import ban should be issued?

Mr. Chesemore, and then we will hear from you, Dr. Sobel.

Mr. CHESEMORE. Any review of studies would be conducted by the Center for Drug Evaluation and Research. This really is an area for Dr. Sobel to respond.

Chairman WYDEN. Doctor.

Dr. SOBEL. Let me say this. We do have investigational drug applications from Dr. Mishell through the Population Council. We have had other applications, as you know; Dr. Nieman's application; Dr. Chrousos'.

I think again I would like to clarify the decision which was made on the multiple factors which Mr. Chesemore enumerated; they exist on their own as grounds for regulatory action. There were four factors which he mentioned, of which safety was one factor.

You have to remember we have a law that it is unlawful to import unapproved drugs into this country. We have made exceptions precisely for humanitarian reasons to bring drugs into this country. When those, all those characteristics are not satisfied, I think it is wrong to devolve completely in your questioning on the safety issues.

There is a regulatory issue which the agency uses in its judgment that has other factors. As Mr. Chesemore elaborated, the particular exceptions are made, for example, for life-threatening diseases, for diseases or situations where there is no other treatment available. So, to completely devolve on the safety issues as a basis for the compliance for the regulatory action is again crossing lines, and I don't think that is appropriate.

Chairman WYDEN. What studies were used to justify the import ban which said that this drug was a health hazard?

Dr. SOBEL. Again, that import ban was not imposed only for that reason. That was one of the factors that entered into that evaluation. Certainly, in regard to pregnancy, we would not want women to be exposed to situations where they might undergo severe bleeding complications in an unsupervised environment. If you want to point to one safety factor which in my mind is paramount, that is it.

I think the drug is a drug with many actions, including antiglucocorticosteroid actions and possibly other actions. It certainly is a drug that has great promise in other areas.

The agency has no intention and never meant for this to happen. Even in regard to abortion, the agency has not taken a position of stopping investigational use. Merely, the agency has taken a cautionary position of making sure that it is used in appropriate circumstances that ensures the safety of women who may elect to take it.

Chairman WYDEN. Mr. Chesemore, I can't find any scientists that you all talked to. I can't find any studies that were relied on for the importation ban. The only thing that I can find is that you all were concerned about newspaper stories.

You were concerned about publicity which somehow would create a great demand for the drug, and then people, even though there had never been any surreptitious entry documented, then people would be gathering this drug around the world, putting it in their suitcases, and rushing to the United States.

Where in our statutes does it say that we are going to base decisions of these kinds on the basis of publicity and newspaper stories? Where in our statutes does it mention that as a reason for basis public health policies?

Mr. CHESEMORE. I am sure we would have great difficulty discovering that particular statute, Mr. Chairman. Indeed, 3 years of experience, I think people in the agency have seen where publicity has been the result of products being imported in this country that were not approved in this country.

You have to take those factors into consideration. Again, it was the intention of this to be only on a personal importation policy and no intention of impacting upon legitimate research of this product.

Chairman WYDEN. Let me go at this point to the particular documents that we would like to focus on. I think you have a set of them. I want to just go through them with you. Exhibit A is a document by the Acting Commissioner, Mr. Benson, the Senate Secretary for Health, dated March 10, 1980.

This briefing memo was designed to bring the Assistant Secretary up to date on FDA regulatory activities on drug and, as far as I can tell, signaling how the agency seems to really make policy, was spurred by a Washington Post editorial involving the import ban.

Here again, we have Mr. Benson making a statement—I can't find any support for it—that the ban was imposed because he believed the publicity would lead to importation.

He makes no references to black market. He makes no reference to the fact that the Roussel-Uclaf restrictions on distributing the

drug were not working. Could you take a look at this memo and tell us how Mr. Benson came to the conclusions he did?

Mr. CHESEMORE. I think that we also have to remember there is one item that has not been mentioned, and that was we also issued something in 1988 called an import bulletin which is an early informational piece to our field. That indeed did follow. This was in 1988 when there was a lot of concern with respect to the importation of unapproved products in this country. I believe, on a particular weekend in June 1988, there was publicity. I think there was a lot of concern. There was publicity with respect to RU 486 and its issue as an abortifacient. As a result of that, we did issue an import bulletin. Sometime later, we issued an import alert, but primarily for the same purposes.

As I stated earlier, there are instances of unapproved products coming into this country clandestinely. We were concerned about that because we were concerned about individuals taking this drug without proper supervision.

Chairman WYDEN. Again, you are citing the publicity factor which, again, seems to be inducing a rationale for making——

Mr. CHESEMORE. Mr. Chairman, many products are ordered based upon publicity and ads put in the paper, et cetera. That was a condition we took into consideration.

Chairman WYDEN. But how were people going to get it except under these tightly controlled circumstances that Roussel-Uclaf has established? The most charitable thing that I can say about your policy is it is overkill because nobody is going to be able to do this anyway. The company tightly restricts it. You gathered no evidence that would suggest that the company or individuals were not complying with it.

I assume you are not calling our doctors dishonest, that they somehow would try to get around these rules. I mean, what evidence do you have, or did you have at the time of the import alert, that would suggest tight controls were going to be violated?

Mr. CHESEMORE. Because the product was unapproved in this country, we had no evidence of what might happen in this country, Mr. Chairman. We certainly were aware of the tight controls that were in existence in France.

Chairman WYDEN. If you had looked, you would have found that the only way you can get it is under these tightly controlled circumstances. This great fear that you had couldn't materialize because the drug couldn't get out that way.

Mr. CHESEMORE. We did have IND's in existence at this time. Any product that would have come in for research purposes would have been allowed into the country.

Chairman WYDEN. I can't believe that you are suggesting that researchers who have IND's would give the drug out illegally?

Mr. CHESEMORE. Absolutely.

Chairman WYDEN. How would it get out? Don't they have to establish tightly controlled circumstances?

Mr. CHESEMORE. Absolutely. That is the way the drug should be——

Chairman WYDEN. I think all of this is awfully creative kind of imagineering here, Mr. Chesemore. I just would like to see some proof on any one of these counts—black market, surreptitious

entry, scientists that you talked to. On every single count, you all basically decided to wing it on this. I think that is what Roussel-Uclaf and our researchers are so unhappy about.

Mr. CHESEMORE. Mr. Chairman, we certainly didn't——

Chairman WYDEN. You show us some evidence that would indicate otherwise.

Mr. CHESEMORE. We have an elaborate process that we do subject these import alerts to for issuance. Ms. Barnes might comment on that.

Ms. BARNES. Even if FDA had not issued an import alert, we still would have detained this product had we detected it coming across the border for abortion use by individual patients. Each individual district, being well aware of FDA's discretionary policy, would have determined this was not a suitable candidate for the policy. The worse that could be said about the alert is that it was overkill. If the product never comes in, no one has a chance to apply the alert. No harm was done.

The product was not suitable for the narrow discretionary exception to FDA's law, which Congress has not seen fit to change, which says that unapproved products should not come into the country until they go through the safety and efficacy testing and are approved through the typical mechanisms.

FDA has done nothing to stand in the way of bona fide research into the product. It has not stopped the company from providing the drug to those conducting research. The only thing we have done is notify our district offices that if they see personal-use quantities for use as an abortifacient, in those situations, it is not befitting that they use that narrow discretionary option to allow its admission. It is a small action the agency has taken in issuing an import alert that has been blown out of recognition to those of us who work in the import area.

Chairman WYDEN. I again would say charitably that it was overkill. It seems to me that what you did was jack up the enforcement system, sent a message around the world without any evidence of a threat. I want to go through some of these other documents. I think the thing that is remarkable about paper is that it can't distort events. There is some interesting paper associated with this import ban.

Exhibit B, the handwritten version of the import alert signed by Marvin Blumberg, on clearance date May 25, 1989, this is 19 days after demand by some Members of Congress that you impose an alert.

Mr. Blumberg makes a statement in the memo that the FDA, "is establishing a 'position' on RU 486 due to 'numerous inquiries' to his office from"—again the memo doesn't make this clear.

We have again queried you all as to the record of these numerous inquiries and have not been able to obtain anything that would indicate that there were any inquiries at all. Now, can you enlighten us on this? I gather that one of your most recent statements says that there were some telephone calls.

Mr. CHESEMORE. That is my understanding, yes, both from our district office as well as, I guess, calls to other parts of the agency wanting to know what the agency's position was on Roussel-Uclaf.

Chairman WYDEN. Any telephone logs that would indicate these calls, any documentary proof?

Mr. CHESEMORE. If it is a call from a district office, it is probably not logged in.

Ms. BARNES. I can say from experience, what typically happens in this situation where you have a lot of press coverage of a particular product, that is in this case an unapproved drug, the district offices, they know people in the import branch. It is quite a routine matter to pick up the phone, call people, and say, "We have heard about this drug, and we have read some of the publicity. Is this going to be a narrow situation where we might use our enforcement discretion or are we going to enforce the law which says it is an unapproved drug and it shouldn't come in?" Those calls are routine.

Chairman WYDEN. I find it hard to believe there were numerous inquiries and absolutely no records from anywhere in the file when your own people say that this was the basis for establishing a position.

Exhibit C is a letter from former Commissioner Frank Young to Jesse Helms. This assures the Senator that the FDA does not condone personal importation of RU 486. It is dated April 17, 1989, a few months before the import ban. The letter states that the FDA believes the drug to be unsafe or at least subject to abuse. It cites problems involving side effects such as nausea, vomiting, uterine bleeding. I would be interested in what specific supportive evidence the agency had for the conclusions drawn in this letter.

Mr. CHESEMORE. The same position that we have stated previously, Mr. Chairman. Our statements are indeed consistent from letter to letter. We certainly just felt that the personal importation of this drug was a very serious situation.

Chairman WYDEN. We certainly just felt like the personal importation of this drug was very serious. Isn't that an arbitrary statement? I mean, I just repeated to you what you said. We certainly just felt like this was a very serious matter.

I feel like lots of things are a very serious, but you all are making drug policy in an area that is very controversial, where people have strong feelings. I think you heard earlier one of our witnesses said she was extremely antiabortion, but was outraged about the fact that has derailed so much research in this country. You are basically offering management by intuition to the American people; aren't you?

Mr. CHESEMORE. No, sir. I believe that indeed we applied our criteria for the importation of unapproved drugs by persons in this matter. As I said, or indeed for research purposes, no restriction was placed on the importation of RU 486.

Chairman WYDEN. Exhibit D is a letter to an unidentified correspondent from Diane Walker, the FDA's Consumer Safety Officer. Now, this one is dated November 28, 1988, 7 months prior to the import ban, and it states that the FDA is issuing IND's for medical research with the drug because it has determined RU 486 is reasonably safe.

Now, this is a statement from the FDA's Consumer Safety Officer, Diane Walker, November 28, 1988, 7 months before the import ban. Your people are saying that this drug is reasonably safe.

She says it is reasonably safe. I have asked for evidence between that time and the time of the import alert, black market, surreptitious entry, taking the drug outside controlled circumstances.

Why the ban when you can't show us any evidence between November 18, 1988, of problems and your own people said on November 28, 1988, that this drug was reasonably safe to administer to humans?

Mr. CHESEMORE. Mr. Chairman, I believe the letter also points out that this is under controlled circumstances under an investigation of a new drug. Indeed, under those controlled circumstances, we were allowing importation of the product.

Chairman WYDEN. But the point is that you are making a conclusion in the November 28, 1988, letter, that the drug is reasonably safe, and then you are making another conclusion 7 months later that the drug is a health hazard, and even though there is no quarrel here that an IND is different than an import ban, I would like to see the proof that caused the agency to make the leap in some months from saying the drug was reasonably safe to saying a drug is a health hazard.

Mr. CHESEMORE. It's simply that the drug has more opportunity to be controlled, an investigational new drug. Those controls did not exist under personal importation, and that's what the drug alert was for, Mr. Chairman.

Chairman WYDEN. But it would be possible, would it not, if you just, hypothetically speaking, set up very tight controls. I mean there are a whole host of ways you can do it. It has been done for Accutane; it's been done for barbiturates. There are ways to set up tight controls, and I can't find any evidence that you all looked at a system of tight controls, either, Mr. Chesemore. Is there evidence on that point?

Mr. CHESEMORE. Mr. Chairman, I think that, indeed, those instances you cite are on approved drugs in this country, and on approved drugs where we know all the safety and efficacy that we need to know. We can make those kinds of decisions. This was a case where, as I said, we had not seen all the safety. We did have concerns about personal use safety.

Chairman WYDEN. Did you look at establishing any controls for drugs that would have been unapproved, so that perhaps we could have not run into this problem?

Mr. CHESEMORE. We believe that the controls under an IND are, indeed, what has been established in this country. That's a long- and well-established policy that we've been operating under.

Chairman WYDEN. The letter dated May 5, 1989, 19 days prior to the signing of the initial import ban, is, I think, also an important one. Besides demanding an immediate ban on the drug, a demand that you complied with within 30 days, the letter raises questions regarding the probability of mail order purchase of the drug. Now, it also criticizes the FDA for allowing any abortifacients into the country, RU 486 or otherwise. It talks about the risks of complications.

Again, all of this without any evidence that we can see in the record. But what strikes me is that it hits very close to not only the conclusions, but also the actual language of agency documents supporting the ban, and even in the actual ban announcement. Now, is

this just a coincidence, or are we letting Mr. Helms just write these decisions?

Mr. CHESEMORE. Mr. Chairman, I don't believe that we are letting Senator Helms determine what the policy is. As you know, I think the subcommittee has records that show we indeed started drafting this policy many months before this. As a matter of fact, as I mentioned, we issued an import bulletin in June 1988, and we also had our guidance in place in June 1988. The import alert really, I guess, went along with that guidance.

Chairman WYDEN. But the fact is that antiabortion groups, and Senators, and Members of Congress who were supportive felt that it was very unclear in early 1989 what the status was of RU 486. You all moved very, very fast to respond to their concerns. I said it was a land-speed record, and I think I am going to use it in instances where I want to have queries answered by FDA for——

Mr. CHESEMORE. Mr. Chairman, we try to respond properly to all Members of Congress.

Chairman WYDEN. You have never treated this Member unfairly, but nobody in our office has ever gotten a response within 30 days. Is it a coincidence that the language was substantially that of Senator Helms' letter?

Mr. CHESEMORE. I think, indeed, we go back to what was in our pilot guidance, Mr. Chairman, back in September 1988, and a number of the factors that I talked about that we indeed consider prior to the importation for personal use.

Also, at the time that we were writing to Senator Helms, I'm sorry—I don't have the response in front of me—but I know that we have always believed and concurred in what the AMA statement was, that indeed we would carefully consider any IND and new drug applications submitted to the agency based upon its merits.

Chairman WYDEN. Now, exhibit F, that is the issued import alert, dated June 6, 1989. One part of that alert has elicited some special concerns by medical researchers. Under instructions, the line reads, and I quote: "Automatically detain all shipments of unapproved abortifacient drugs," and the concern among medical researchers here, is that now we may be out beyond just RU 486. Could you tell the subcommittee how many drugs are encompassed in what seems to be a very sweeping action?

[Exhibits A through F, referred to above, may be found in the appendix.]

Mr. CHESEMORE. I think I mentioned earlier, Mr. Chairman, we have some 58 import alerts on various human drugs, if that responds to your question. Some of those are indeed unapproved in this country.

Chairman WYDEN. But how many abortifacient drugs? I mean, this statement says, "Automatically detain all shipments of unapproved abortifacient drugs." What are we talking about here beyond RU 486? I think this is important, and I would like to know specifically what abortifacient drugs we are talking about here.

Mr. CHESEMORE. I will ask Dr. Sobel to expand on my response. I'm aware of one other particular compound, something called tricosanthin compound Q that is used in China as an abortifacient.

We also have an import alert on it. The other drugs are other unapproved drugs, unless Dr. Sobel knows of other ones.

Dr. SOBEL. I don't know of any others, except as a part of a general category of abortifacient drugs with a separate regulation, but I don't know of any specific compounds, other than RU 486.

Chairman WYDEN. Wouldn't we be talking about possibly hundreds of drugs, because this could be any drug with abortifacient properties, couldn't it? I mean, it seems to be a very sweeping statement, and certainly touches on some of the concerns of our researchers, in that more and more we are going to be seeing drugs with multiple benefits. Doesn't this touch possibly on hundreds of drugs?

Mr. CHESEMORE. Mr. Chairman, again, if there is an IND established for a drug, we would not detain that product from coming into the country. It could go on to its research use.

Chairman WYDEN. Tell me if you all feel that the controls that Roussel-Uclaf has established for RU 486 are inadequate.

Mr. CHESEMORE. I'm not sure that we've even had an opportunity to evaluate those controls.

Chairman WYDEN. Dr. Sobel, I want to hear from you in just a second. But Mr. Chesemore, you have issued an importation ban on the grounds that it is a health hazard because this drug could get into the United States and not be supervised. But yet you tell us that you haven't even looked at, or analyzed what Roussel-Uclaf is doing. Now, how can that be even——

Mr. CHESEMORE. I'm sure that they have excellent controls in France. Our concern would be, is that product getting out of France somehow, and when it does, how is it coming into this country.

Chairman WYDEN. You have no evidence of that either.

Mr. CHESEMORE. Not at this time.

Chairman WYDEN. No evidence whatsoever.

Mr. CHESEMORE. No; apparently their controls are working quite well.

Chairman WYDEN. Dr. Sobel.

Dr. SOBEL. Their controls seem to be very good; they are very careful about making sure the drug doesn't get out. However, whether this will be an ongoing process, we don't know. The United Kingdom, Scandinavian countries, and I believe Holland, are planning approvals, so to base a decision at one point in time in one set of circumstances is difficult.

I agree with you. The chance for this drug getting loose from France, so to speak, would seem to me from what I've heard and from discussions with people who know how it's given, is very small. But I don't think that that's the purpose of the import alert; it's establishing a principle which can respond to changing conditions overseas. I mean, we can't regulate by the international telegraph. We have to say, we are justified in imposing that, even though we acknowledge the conditions in France are excellent for distribution.

Chairman WYDEN. But your point, Dr. Sobel, is not responsive to my concern. You are saying that things seem to be fairly well controlled in France.

Dr. SOBEL. Very well controlled.

Chairman WYDEN. The point is Roussel-Uclaf, the manufacturer of the drug, has been very blunt, been very specific, that they will give this out only under very tightly controlled circumstances. So, what's relevant here is the company, not the country, and it is well-controlled France.

Do you have any evidence that you can give us that Roussel-Uclaf is not taking this very hard-nosed, restrictive position on controlling this drug?

Dr. SOBEL. I think you are absolutely correct to a fault, because we have situations where we've had investigators who want to bring in the drug, and I can't mention the IND, because that's not publicly disclosed, where Roussel-Uclaf has refused to give the drug.

So, talk about overkill, as we did before, I think we have to keep the lines straight, what the FDA's contribution is, and what Roussel-Uclaf's contribution is.

Chairman WYDEN. I think the lines are now very straight. You have said that Roussel-Uclaf certainly has an air-tight system for controlling this, is making sure that it's not getting out in an unsupervised way, and yet without any evidence whatsoever, the FDA said——

Dr. SOBEL. I think that——

Chairman WYDEN. Excuse me for a second. Without any evidence whatsoever, the FDA, even though Dr. Sobel and possibly others say Roussel-Uclaf's system is air tight, the import ban is going to be based on the fact it could be used in an unsupervised way. I think this is an absurd position for this agency to take.

Dr. SOBEL. I don't understand exactly what you've said. I say very clearly that Roussel-Uclaf has been very responsible in its administration of the drug in France, and indeed, had to be urged by the French Government to make the drug available, even under those circumstances, because of whatever pressures existed in France.

However, our policy has to cover the circumstances as they may develop, and that is the purpose of the policy. In other words, an ongoing condition of tight control is not necessarily guaranteed, and ours reflects our regulatory structure.

Chairman WYDEN. Excuse me just for one second. Describe for me the scenario that would cause a problem in the United States, Dr. Sobel. I mean, you've told me——

Dr. SOBEL. I really, frankly, don't believe that there is a strong scenario for importation from France of this drug for pregnancy. But that does not make the implementation of an import alert unnecessary or illogical.

I agree with you, that it's unlikely for a woman to discover she's pregnant, and then within—she has to take the drug within 7 weeks of her last period, so, say, in the fourth week she misses a period and in the fifth week becomes concerned and establishes she's pregnant, she's not going to start an international correspondence for the drug when there are other good methods of inducing therapeutic abortion in the country.

So, I think if you are trying to subject the policy to a scenario-type of situation, I think we will fail in our defense. What we are trying to do is say, is this position based on regulatory policy, with

the characterization of when this breach of the statute is permitted, then we haven't failed. We have applied it exactly correctly, and legally, and I wish our legal counsel would address that.

Chairman WYDEN. I am going to——

Ms. BARNES. Mr. Chairman, if I may——

Chairman WYDEN. As a practicing lawyer, you can recognize a statement against interests, but that was sure what we just heard from Dr. Sobel. Dr. Sobel just said point blank that he couldn't describe a scenario——

Dr. SOBEL. I could describe a scenario. I cannot foretell what is going to happen. I'm not a prophet.

Chairman WYDEN. Describe a scenario for me.

Dr. SOBEL. The scenario is that when this drug is distributed in countries other than France, becomes available in the world market, and becomes available through whatever process to be imported into the United States and widely distributed, without supervision? Just as I'm willing to agree to your arguments, I think that there are valid arguments on the other side, too, that when one implements a regulatory policy, one is regulating according to certain stipulations of the law.

Chairman WYDEN. Ms. Barnes.

Ms. BARNES. I just wanted to comment that the ban against bringing this product into the country is the statute. The statute says, unapproved drugs may not come into the country. That's what FDA is dealing with. That's the ban on this drug. It's not the import alert. FDA has said over time that it came up with its import policy primarily to deal with AIDS drugs. In certain situations, in very limited situations, FDA will occasionally allow in a drug for certain serious and life-threatening conditions where an alternative does not exist.

For example, someone is coming into the country, they are dying of AIDS, they have an AIDS remedy with them, there is no effective AIDS treatment in this country, FDA uses its discretion occasionally to let those drugs into the country.

Until Congress changes the statute to set up an alternative mechanism for people who want to bring drugs in for their own use in this kind of situation, FDA has no other choice but to enforce its statute, and what it does here is consistent with its statute. We have in no way stood in the way of any legitimate research being conducted on this product, nor would we.

Chairman WYDEN. Why, when this is a discretionary process, which I don't think is disputed by anyone, why was RU 486 singled out?

Ms. BARNES. It wasn't singled out. We have numerous other alerts. For example, when Retin-A was in the news and people were bringing it in, THA, there are a number of products, there are 58 alerts in total relating to drugs. You will see that RU 486 is totally consistent with every other situation in which we've issued an alert.

There was nothing unusual about how the alert was cleared and put out in terms of how it met what we had established as criteria for evaluating use of our discretion.

Chairman WYDEN. Once again, Ms. Barnes, I think we are highlighting the differences. People were bringing in Retin-A. There

was actual personal importation. Nobody is bringing in RU 486, according to Mr. Chesemore, but he is concerned that maybe we will have some publicity and somebody will eventually try and do it, and so we ought to make a policy for that reason.

Let me move on, Mr. Chesemore, to a couple of the other concerns that were raised by the scientists. Dr. Regelson and several others were concerned that development of other drugs might be hampered because they were drugs with multiple benefits, abortifacients and drugs that could help against cancers.

Are you troubled by the fact that we are starting down a path here with RU 486 that could be repeated with a wide variety of other drugs? That you could be sitting here in front of other Members of Congress raising concerns about other kinds of drugs, unless there is a resolution of this?

Mr. CHESEMORE. Mr. Chairman, of course we do not want to do anything to get in the way of legitimate research on drugs in this country. Again, I believe our policy does not impact, should not impact on legitimate research and the importation of drugs for approved IND in this country. We have a good system. We have a compassionate IND system in this country, and we hope that indeed our policy will have no impact on it.

Chairman WYDEN. I want to ask the question again and see if I can get a responsive answer. Are you concerned, because Dr. Regelson and the scientists raised it in the beginning, that this is the kind of thing that can happen again and again, because there are other new drugs that might also be abortifacients and have other multiple benefits?

Mr. CHESEMORE. Absolutely, we are concerned, sir.

Chairman WYDEN. All right. Dr. Regelson also made another point that I found very persuasive and very important, Mr. Chesemore. He said that FDA is supposed to be acting like an advocate, and not the kind of obstacle that the scientists have seen, to research. What is FDA going to do now to try to turn this situation around? Because any way you slice it, Dr. Chrousos, and others, who are doing work that you have said you think is important, and I think is important, and I am sure millions of Americans think is important, that work is coming to a halt. I mean, it isn't going forward. He is not able to take on new people, and he is concerned about whether he is going to have enough RU 486 to handle people that he has got.

What is FDA going to do now, November 19, walking out of this hearing room, to address this situation, turn it around, and, in the words of Dr. Regelson, be an advocate for medical research and those who are suffering, rather than the obstacle that the scientists have described?

Mr. CHESEMORE. Mr. Chairman, I think the Food and Drug Administration has been an advocate for research for decades. Certainly there are situations where, in the orphan drug research area, for example, we are indeed advocates for researching drugs; we indeed have a process here for investigational drugs, compassionate drugs.

We want to do everything we can to make sure that people understand what our policies are. I was disappointed today that indeed some people don't know what the policies of the agency are.

I think it's incumbent upon us to do what we can to make people in the research field know what this policy is and how to get drugs for investigational use, and in the laboratory setting, as Dr. Horwitz described. Unfortunately, I think sometimes, we have poor communication problems, and I think that happens with any large organization. We need to do a better job there.

Chairman WYDEN. But you have said you have got a process, and the scientists and the patients who have come here today have said the process is not working. Dr. Chrousos is not a politician. Dr. Chrousos is a scientist who wants to make sure that he gets enough RU 486 in order to do the research that he feels is necessary. Dr. Horwitz is not a politician. She also is concerned that she is going to get the RU 486 that she needs.

So, the process that you have described is not working. The research is not getting done. What is the agency going to do now to turn this around besides saying, we've got a process and that's going to take care of things.

The testimony that we had earlier today indicates that the process is not working, and that what the scientists said was that their patients are certainly being punished for two reasons: FDA policies and the views of this company to not want to get involved in controversy. What are you going to do to try to turn it around?

Mr. CHESEMORE. It's indeed not the authority of FDA to make these corporate decisions that these companies have to make. We have indeed approved the legitimate uses for research of these products when proper application comes to our attention, Mr. Chairman. We will continue to do that. Indeed, we would encourage this manufacturer to continue with the processes that are approved, and with these IND that are approved for the use of research into RU 486.

Chairman WYDEN. Mr. Chesemore, would it be fair to say that no one currently is banging on FDA's door seeking new IND permits to use RU 486?

Mr. CHESEMORE. I really couldn't say.

Chairman WYDEN. Dr. Sobel, that's a fact; isn't it?

Dr. SOBEL. We haven't had a lot of IND's submitted recently, but the one we did have submitted failed primarily because Roussel-Uclaf would not supply the drug.

Chairman WYDEN. But how can we——

Dr. SOBEL. We were willing to go right ahead with that IND, by the way.

Chairman WYDEN. How can we then say that the process is working? I have been very clear today that I think that there are three factors at issue here. I think that FDA's arbitrary policies have contributed significantly to this problem. I think that anti-abortion politics have contributed significantly to this problem. I think the company's business judgment to steer clear of the United States has been a factor. But I still have not heard anything that the FDA, the premiere regulatory agency in the drug development field is going to do to turn this situation around. Before we leave, I would like to hear of some step that the FDA thinks is worthwhile to try to address this. Because it is now a fact, it is part of sworn testimony, that research can't go forward. In answer to our last question, we established that there seemed to be few, if any, I

gather one, according to Dr. Sobel, new IND permits—new IND applications that are——

Dr. SOBEL. Let me modify that. My administrative officer told me 4 days ago there was a request for a compassionate IND for a patient with meningioma, and it was granted immediately. So, there is no reluctance on the part of the agency to stimulate research.

Chairman WYDEN. We hope that it is the first of many, and I appreciate that. But, again, how can we say that the process is working after we have heard from the scientists, after we have heard that, I guess now we are up to two IND's coming in as opposed to the 10 that we used to have?

I find it hard to see how we can say the process is working, and I would still like an answer to the question, Mr. Chesemore, and if you want to say we are not going to do anything so be it. We hear the kind of testimony that has been given today; we have listened to the scientists; we have listened to the patient advocates. We are going to try to get Lou Sullivan on the phone to Roussel-Uclaf, and see if we can get additional RU 486 in order to do this research.

I think what the American people want the FDA to do is what Dr. Regelson said earlier, and that is to be the advocate, to be out in front, rather than to be the identified obstacle that the researchers and the patients have described today.

So, let's give this one more shot, and if you want to say you aren't going to do anything, then we can walk on out of here and say that you aren't going to do anything. But I want to give you one last chance to respond to the thoughtful point that Dr. Regelson made, which is that we want you to be the advocate and try to turn around a process that clearly is not working.

Mr. CHESEMORE. Mr. Chairman, indeed, the Food and Drug Administration wants to do everything that we can, within the laws in which we administer, to not impede legitimate research on RU 486 or any other drug in this country. We do have a good process. We have a number of drugs that are indeed being tested in this country today because of the good processes of the Food and Drug administration, and because we indeed have been advocate.

The fact that in this particular instance that process seems to have slowed down, I believe is the Food and Drug Administration's responsibility to again announce that we are more than willing to carefully review any application that comes forward. That is what our job is, sir.

Chairman WYDEN. I think this has been a very informative panel, and I have to tell you that I think that the position of the FDA is very unfortunate. It is one issue to debate abortion, and reasonable people have differing views with respect to abortion. But what we are talking about here is not abortion. What we are talking about here is that in the name of taking a symbolic kind of action in response to a problem that doesn't exist, or at least can't be supported by FDA files, critical medical research is being derailed.

I am of the view that Americans are going to suffer needlessly as a result of this position. I would just ask you to go back and review the kind of testimony that you heard today. It is one thing to be opposed to abortion, but what the FDA has done here is to go way beyond the abortion issue, and set in place, I think, an approach to

science that is going to be very dangerous, that has implications even beyond RU 486. Because other drugs will be used as abortifacients and have multiple benefits as well.

I would like to see you go back to doing it by the book. I would like to see you go back to doing it as the American Medical Association said earlier, which is that if drugs meet the standards set out by our Congress, they are approved. If drugs don't meet the standard, they aren't.

For goodness sake, knock off this approach that we are going to make drug policy on the basis of publicity. I have been up here involved in health issues for 10 years, and I think of the last time where Federal regulators said that on the basis of a nonexistent threat. I don't find that anywhere in the statutes, and I think it is very irresponsible.

If you would like to add anything further, we will be happy to hear it, and otherwise, we will adjourn.

Mr. CHESEMORE. Thank you, Mr. Chairman.

Chairman WYDEN. The subcommittee is adjourned.

[Whereupon, at 1:30 p.m., the subcommittee was adjourned, subject to the Call of the Chair.]

APPENDIX

News From
Congressman
RON WYDEN

THIRD DISTRICT
OREGON

2452 Rayburn House Office Building * Washington * DC * 20515 * (202) 225-4811

PRESS ADVISORY
THURSDAY, NOVEMBER 15, 1990

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HAS FDA'S IMPORT BARRIER ON FRENCH ABORTION PILL RU 486
STALLED U.S. RESEARCH AGAINST LIFE-THREATENING ILLNESSES?

CONGRESSIONAL HEARING INVESTIGATES EFFECTS OF HILL PRESSURE,
ANTI-ABORTION LOBBYING, ON KEY FEDERAL AGENCY

Rep. Ron Wyden Calls Ban
"Politically Motivated"

WASHINGTON, D.C. -- Potentially life-saving research on breast and brain cancer, Cushing's Syndrome, and other dread diseases is being stymied in the United States due to a politically driven Federal ban against the French abortion drug RU 486, Rep. Ron Wyden, D-Ore., said Thursday.

"Tens of thousands of Americans, including 43,000 women who die each year from breast cancer, could be helped by therapeutic use of RU 486," said Wyden. "Instead, important clinical trials of this new drug are being shut down all over the country because of federal agencies more interested in caving into political pressure groups than in shepherding good science."

The Subcommittee on Regulation, Business Opportunities and Energy, which Wyden chairs, has been investigating actions leading to the Food and Drug Administration's decision last year to ban importation of personal quantities of the drug. Wyden said evidence collected by the subcommittee to be presented at a scheduled November 19 hearing indicates that the Food and Drug Administration has not presented sufficient evidence to justify its alert on health and safety grounds.

Wyden said, "There is significant evidence in the agency's files demonstrating that FDA moved quickly to restrict access to RU 486 after being lobbied hard by both anti-abortion interest groups and their political supporters on Capitol Hill."

Wyden said that the basis for the alert -- which has effectively ended U.S. clinical research on the drug -- will be examined during a congressional hearing, time and place as follows:

Time: 10 a.m.
Date: Monday, November, 19, 1990
Location: 2359 Rayburn House Office Building
Place: Washington, D.C.

Wyden said the subcommittee will hear testimony from a panel of FDA witnesses, U.S. clinical researchers including scientists from the National Institutes of Health who have used the drug in clinical trials, the American Medical Association, and others.

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101st Congress

United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Energy
B-363 Rayburn House Office Building
Washington, DC 20515
HEARING

SMALL BUSINESS SUBCOMMITTEE ON
REGULATION, BUSINESS OPPORTUNITIES AND ENERGY

HON. RON WYDEN
CHAIRMAN

MONDAY, NOVEMBER 19, 1990
WASHINGTON, D.C.

RU 486: THE IMPORT BAN AND BASIC MEDICAL RESEARCH

WITNESS LIST

PANEL 1

Dr. William Regelson, M.D.
Professor of Medicine
Medical College of Virginia
Richmond, Virginia

Dr. Kathryn Horwitz, Ph.d
Professor of Medicine
University of Colorado
Denver, Colorado

Dr. George P. Chrousos, M.D.
Section Chief, Pediatric Endocrinology
Developmental Endocrinology Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

Dr. Lynette K. Neiman, M.D.
Developmental Endocrinology Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

PANEL 2

Wanda L. Guesnier
Lubbock, Texas

James F. Nelson
Flemington, New Jersey

Andrea Hecht
President
National Cushing's Association
Sherman Oaks, California

Beverly Zakarian
President
Cancer Patients Action Alliance
New York, New York

Helen Byrne
Vice President
Cancer Patients Action Alliance
New York, New York

Dr. Myron Allukian, D.D.S.
Past President
American Public Health Association
Boston, Massachusetts

Representative of the American Medical Association

PANEL 3

Ronald G. Chesmore
Associate Commissioner
Regulatory Affairs
U.S. Food and Drug Administration
Rockville, Maryland

Dr. Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research
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Sandra Barnes
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101st Congress

United States House of Representatives
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November 1, 1990

TO: Chairman Wyden, Subcommittee on Regulation, Business Opportunities and Energy

FROM: Subcommittee Staff

SUBJECT: Hearing Memorandum

Federal Import Restriction of the Drug RU 486 Has Hampered Life-Saving Research into Dread Disease

Scant Scientific Data on Adverse Health Effects Fails To Support Barrier

INTRODUCTION

Earlier this year, subcommittee staff began an inquiry into the June 6, 1989, federal import ban on the controversial French drug RU 486. This investigation focused on allegations raised with the subcommittee by members of the health research community that this ban had slowed or stopped crucial medical research being undertaken, planned or proposed using the new drug.

The research in question involves treatment of diseases such as Cushing's Syndrome, breast and brain cancer, hypertension, diabetes, and acquired immune deficiency syndrome (AIDS). Together, these diseases account for thousands of deaths in the United States each year. According to a number of scientists, including research project leaders at the National Institutes of Health (NIH), RU 486 may have significant value in the treatment or cure of these diseases, and, in fact, may be the most important new drug for treatment of these life-threatening conditions.

But investigation into treatments using this drug, which is also prescribed in Europe as an abortifacient, has been slowed -- in some cases, stopped altogether. Researchers questioned by subcommittee staff blamed declining scientific inquiry on a combination of (1) the Food and Drug Administration action banning the importation of personal quantities of this drug because of its alleged safety hazards, and (2) a foreign manufacturer which has virtually abandoned new medical research projects in this country, using RU 486, as a result of rising opposition from anti-abortion activists.

The Food and Drug Administration (FDA) in recent years has issued special permission to ten research groups -- including one at the NIH -- to use the drug in clinical investigations. And according to the FDA, although only "two or three" of those projects involved use of the drug in pregnancy termination studies, most of the projects, some of them involving treatment of life-threatening disease, now appear to have been discontinued.

The hearing, scheduled for November 19, 1990, will examine several staff findings:

1. There is an obvious relationship between the import ban on personal quantities of RU 486 and the reluctance of the drug's manufactures to seek approval for commercial distribution of the drug in the United States, or provide sufficient quantities for research purposes.

2. A review of the FDA files and of available scientific data indicates that there is little substance to the Food and Drug Administration's claim that RU 486 "poses unacceptable safety risks to the American public."

3. Coupled with the lack of scientific data supporting health risk concerns, the timing and character of correspondence between FDA officials and anti-abortion activists prior to the import ban indicates that the agency's decision was motivated by politics rather than by science or a desire to protect the public health from a clear and present danger.

4. Despite the fact that the import alert does not directly impact FDA-licensed research projects using RU 486, the restriction has had a significant chilling effect on the relationship between the drug's manufacture and U.S. medical researchers. The import ban has effectively ended most research involving deadly and debilitating illnesses with the drug in this country.

5. The drug's manufacturer is concerned that U.S. government opposition to RU 486 will force the World Health Organization (WHO) to withhold worldwide approval for the drug. The company stated that W.H.O. will not sponsor the drug's distribution because of the possible retaliatory loss of U.S. financial support in retaliation. Without W.H.O. sponsorship, many Third World nations could lose access to a safe, efficient and cheap means of pregnancy termination.

Staff concludes that:

1. A combination of politically inspired opposition to this drug as an abortifacient by key federal agencies, and the obvious reluctance by the drug's manufacturer to attract more intense pressure from anti-abortion forces by making it available to medical researchers jeopardizes the lives of tens of thousands of Americans suffering from diabetes, cancer, Cushing's Syndrome and other illnesses.

2. The breakdown of clinical research using this drug in the United States could short-circuit discovery of cures or effective treatments for a variety of fatal illnesses which worldwide continue to take countless lives.

3. Finally, concern over antagonizing U.S. anti-abortion groups and the subsequent loss of U.S. financial support may cause the World Health Organization to abandon plans to approve distribution of this drug to Third World populations as a safe and effective abortifacient. Should W.H.O. cave into these tactics, many Third World women would be victimized by death or serious injuries through the alternative use of unsafe abortion practices. Worldwide, these unsafe practices may result in some 200,000 unnecessary deaths per year.

WHAT IS RU 486

RU 486 was first synthesized approximately ten years ago, and it is owned by the French drug company Roussel-UCLAF. The drug is a mifepristone -- a synthetic steroid. As such, its principal value is in the blocking or inhibiting of progesterone and glucocorticoid, naturally produced hormones. Progesterone produced in the lining of the uterus signals the lining to continue to grow after fertilization of an egg. When RU 486 is used as an abortifacient, it inhibits the production of the hormone. The uterus sheds its lining along with the egg.

RU 486 terminates early-stage pregnancy without surgery, but it is only effective in the first eight to nine weeks of gestation. Also for greatest effectiveness, RU 486 should be taken with a prostaglandin, a drug which speeds the shedding of the uterus lining. Neither RU 486 nor the prostaglandin used with the drug in France is approved for general use in the United States although an estimated 65,000 abortions have been performed in France without significant side effects or difficulty using the combination of the two drugs.

Beyond its application as an abortifacient, RU 486's clinical importance is based on its action as a blocking agent to corticosteroid, a naturally produced, anti-inflammatory hormone.

This blocking property has drawn the extreme interest of oncologists and endocrinologists, specialists in the treatment of diseases such as breast cancer, Cushing's Syndrome, diabetes, acquired immune deficiency syndrome and hypertension.

In one clinical trial of the drug among advanced breast cancer cases, for example, 18 percent showed "significant measurable tumor regression to (RU 486)," according to a commentary in the August 22/29, 1990 edition of The Journal of the American Medical Association.

The same article also reports positive results from trials involving treatments of inoperable meningiomas, another form of cancer.

Research at the NIH on the treatment of Cushing's Syndrome, a highly painful and often fatal disease, has also been very promising. Cushing's Syndrome sufferers were treated with large doses of the drug for extended periods of time. NIH reports that a number of later-stage patients are now in remission.

Other researchers believe that RU 486, because of its potential value in modulating viral infection, could be a treatment for Epstein-Barr disease and may also have value in treating AIDS.

> "Medical studies with (RU 486) will not create a prescription-medicated abortifacient 'black market' in mifepristone pills," wrote Drs. William Regelson, Roger Loria and Mohammed Kalimi in the JAMA commentary.
>
> "It is tragic that in this country 43,000 victims die of breast cancer each year," they wrote, "while abject surrender to abortion politics delays clinical studies that might help them. It is time to join the public debate on the ethics of denying drugs to the living because of political activism regarding the unborn."

THE FEDERAL AGENCY POSITION

Distribution

RU 486 can not be distributed commercially in the United States until or unless the manufacturer applies for, and receives, specific approval from the Food and Drug Administration.

Roussel-UCLEF, the manufacturer, has not sought approval. The company is apparently concerned that an application would create a damaging backlash against Roussel UCLEF and its sister organizations in the U.S. and, perhaps, worldwide.

Roussel, whose parent company had sales totaling $6.4 billion in North America last year, is concerned about (1) a possible boycott by anti-abortion activists against company drugs already distributed in the U.S. and (2) the FDA's import alert issued in June of 1989, which barred importation for personal use.

** It should be noted, here, that the drug in Europe is available only through personal prescription from a specifically licensed clinic.

According to correspondence by former FDA Commissioner Frank E. Young, the June 1989 import alert directing customs officials to seize the drug was issued because "the intended use of this drug makes it likely it would be used without benefit of supervision of a physician, and indiscriminate or unsupervised use could be hazardous to the patient's health."

Research:

Under guidelines imposed by Congress and the Administration, the National Institute of Health cannot conduct clinical trials for abortion research using RU 486, or any other abortifacient drug.

Similarly, such research cannot be undertaken under federal grant. There is no such limitation on non-federally supported research.

The NIH, however, can and has supported both intramural and extramural research into other uses and applications of the drug.

Because the drug is not approved for commercial distribution in the United States, the Food and Drug Administration must issue an IND (Investigational New Drug) permit for clinical trials using RU 486. The IND requirement applies to both government and non-government research. According to the FDA, some 10 INDs currently exist for RU 486 research, although most -- if not all -- appear to be moribund.

** Typically, under an IND, quantities of the drug are donated to the individual research group by the manufacturer. The substance of the research and its results can in whole or in part be kept confidential in order to protect manufacturer's proprietary rights.

Three years before his department issued its import alert, then-Secretary of Health and Human Services Otis Bowen commented on RU 486 research in the United States in an April 1986 letter to Senator Gordon Humphrey:

> "In view of the many potentially beneficial health uses of RU 486, I believe that it would be in the best interest of the American people to continue the HHS-funded studies on that compound. I can, however, assure you that no HHS funds have been used to support research on RU 486 as an abortifacient."

** Bowen added, however, that due to the "considerable concern" raised by Humphrey and fellow senators Helms, East, Grassley, Symms and Denton, he would continue "monitoring closely this biomedical research to assure that no support will be provided to RU 486 as an abortifacient."

> Despite its lack of FDA approval, however, there is a chance that RU 486 may be made available in California under recent acts by the state legislature. State officials and the California Medical Association have advocated testing and trials of the drug in the state to enhance research of potential anti-AIDS remedies.

RU 486: SAFETY AND EFFECTIVENESS IN HUMAN TRIALS

RU 486 has undergone clinical trials in several countries, including the United States, both as an abortifacient and for other medical purposes.

France -- where the drug was developed -- has perhaps the broadest clinical experience with the drug. RU 486 has been administered to 65,000 women, with an effectiveness rate of 96 percent. Of the remaining 4 percent, abortions were achieved but the embryo was not expelled and a vacum aspiration was required. The drug failed in 1 percent of cases.

A few women -- between 2 and 5 percent of users -- experienced adverse but generally minor side effects, according to French health officials. Problems mainly were attributed to prostaglandin. The "abortion pill" has been widely hailed in France as a safe and efficient alternative to surgical abortions, and one that offers fewer risks to women undergoing the procedure.

The drug was also employed as an abortifacient in the United States four years ago in a trial which until recently received little publicity. That trial, at the University of Southern California, found the drug to be 90 percent effective even without the use of prostaglandin. Women who had surgical abortions prior to using the drug generally preferred the RU 486 method. Dr. David Grimes, a professor of obstetrics and gynecology at USC, said the drug produced no serious side effects and generally seemed less traumatic than surgical procedures.

The drug's safety and effectiveness also has been endorsed in papers and commentaries published in the New England Journal of Medicine and the Journal of the American Medical Association. The American Medical Association has called for further testing and possible use of the drug.

FDA ACTIONS AGAINST RU 486, KEY CORRESPONDENCE

Despite scant evidence that RU 486 in and of itself poses a health risk to users, or that it would be used without direct supervision by a physician, the Food and Drug Administration--chief gate keeper on drugs made available to the American public -- has taken an extraordinarily hard line against the pharmaceutical.

The agency issued an import alert for the drug on June 6, 1989. The import alert gave customs inspectors the authority to seize personal quantities of the drug upon attempted entry, including by mail, to this country.

> "FDA has concluded," read the alert, "that unapproved products of this kind would be inappropriate for release under the personal importation policy. The intended use of such drugs could pose a risk to the safety of the user."

The FDA has a discretionary policy which allows personal importation of important or unique drugs, particularly those which may have life-saving characteristics, when those drugs are not yet approved for U.S. distribution. In its 1989 action, the agency suspended that leniency despite the fact that (1) in France RU 486 can only be used under a physician's direct supervision in a specifically certified clinical situation, and (2) there had been no seizure cases at that time of any quantity of RU 486 carried or mailed into the United States surreptitiously.

> Later, on January 12, 1990, FDA official Marvin A. Blumberg reported that "concerning FDA detention of pharmaceutical RU 486, we have checked our national detention data for the past two years and have found no reported detention of this product.

There seems to be no scientific or procedural safety issue providing foundation for this FDA action, and no record of attempts to bring the drug into this country. However, the timing of the import alert did coincide with pressure then being brought upon the agency by congressional abortion opponents.

On May 5, 1989, then-FDA Commissioner Frank Young received a letter from 11 anti-abortion activists in the Congress. The letter notes with alarm the FDA's flexible policy allowing individual Americans to "mail order non-approved drugs from overseas for personal use." The letter said that while the "apparent blanket policy is prima facie disturbing overall, one specific concern is that the French abortifacient RU 486 is not one of the 40 drugs specifically excluded" from the FDA personal importation policy.

> "The U.S. government should not be involved in abetting abortion," the letter read. "Are there regulations currently being drafted that would add abortifacients, and specifically RU 486, to the list of prohibited drugs?"

The May 5 letter spawned a flurry of activity at the FDA. On May 23, the agency's Import Operations Branch issued a recommendation that the drug RU 486 was "inappropriate for release under the personal importation policy" because of the likelihood that the product "would be used without benefit of supervision of a physician and indiscriminate use could be hazardous to health."

Three days after the alert was issued, Commissioner Young wrote back to the critical congressmen in a June 9, 1989, letter:

> "We do not believe," said Young, "that this (personal importation) policy can be appropriately applied to the importation of RU 486 because use of the product could present an unreasonable safety risk. That is, the intended use of this drug makes it likely it would be used without benefit of supervision of a physician and indiscriminate or unsupervised use could be hazardous to the patient's health."

Young also cited dangerous side effects such as extensive bleeding for issuing the alert against the drug.

Young's statement and the FDA's new position seems at odds not only with available clinical data on the drug, but also with earlier agency decisions. Seven months earlier in November 1988, Diane F. Walker, consumer safety officer for FDA's Center for Drug Evaluation and Research, wrote this in response to questions regarding RU 486 safety in clinical trials:

> "Before we will permit testing a drug in humans, the sponsor of the drug must provide us with information demonstrating that the drug is reasonably safe to administer to humans.

> "The sponsor must also provide manufacturing and control data, a detailed protocol of study and names and qualifications of investigators who will be performing the clinical trials. These requirements were met (for trials of RU 486) by the Population Council."

The Population Council holds one of ten INDs issued by the FDA for clinical trials of RU 486.

Staff discussions with the FDA have not yet revealed how the agency could conclude that on the one hand for purposes of issuing the Population Council IND, RU 486 is reasonably safe and effective and, on the other, as the foundation for issuing the import alert the drug presented an unreasonable safety risk. The FDA position is particularly hard to rationalize given the restrictions under which the drug is prescribed and administered in Europe (see page seven).

Subcommittee staff can only conclude that (1) evidence indicates that the import alert decision was politically driven and (2) opposition to this drug as an abortifacient by agency heads and their congressional cohorts has had at least an indirect negative impact on trials using RU 486 in the treatment of serious disease.

Staff suggests that federal health policy to date has not focused on encouraging experimentation with a potentially new drug. Rather, it seems primarily targeted at keeping RU 486 out of the United States as an abortifacient, regardless of the cost to those suffering from cancer, Cushing's Syndrome, diabetes or other diseases. It creates a barrier against promising research on a variety of deadly or debilitating conditions. And it appears that the federal government's role as an advocate of important medical research has been seriously compromised.

STATEMENT OF WILLIAM REGELSON, M.D., PROFESSOR OF MEDICINE

Medical College of Virginia
Virginia Commonwealth University
October 26, 1990

The Honorable Ron Wyden
Chairman
House Committee on Small Business

Attn: Mr. Steve Jenning
Subcommittee Staff Director
B-363 Rayburn House Office Building
Washington, DC 20515

Dear Representative Wyden and Mr. Jenning,

As I indicated to you, I would be happy to appear before your subcommittee on Monday, November 19.

I also feel that in view of RU 486's effects in upregulating immunity, and our plans that were thwarted by the embargo to develop a clinical study of RU 486 in AIDS, that a representative AIDS victim or member of the gay community should be there to represent their self interest. I contacted Mr. Jenning in regard to contacting Martin Delany, Director of Project Inform.

In response to your questions:

1. To your knowledge, is there sufficient scientific research available to make the assessment that RU 486 poses unacceptable safety risks?

Certainly in acute studies, which were directed toward the use of RU 486 as an abortifacient, there does not seem to be any serious safety risk.

Similarly, in a more chronic study done as part of a phase I in the treatment of breast cancer and in the treatment of meningioma and Cushing's disease, there were no inordinate side effects that precluded further development.

It is totally inappropriate for the head of the Food and Drug Administration to raise questions as to RU 486's safety that would preclude appropriate phase I and II studies determining its activity in clinical trial.

Department of Medicine . . P.O. Box 273 . . Richmond, Virginia 23298-0001 . . (804) 786-0454

Did the FDA director ask for animal toxicology data? Where is his review; his panel of experts; his in house memos discussing toxicology?

The one feature that one would have to be most concerned with on clinical study is the possibility that RU 486 may enhance fibrosis following injury and/or wound healing which was reported in one rodent toxicology paper. However, again, this is dose and time related and this is certainly not a side effect that one would be inordinately concerned about, but we would have to take under clinical advisement as part of any study. Similarly, one would have to be concerned regarding the reacerbation (recurrence) of arthritis or autoimmune disease, (i.e., asthma, lupus) that are controlled by corticosteroid action.

Certainly, the essence of any evaluation of a drug is based upon therapeutic index. In studies of Cushing patients and in patients who received the drug for the treatment of meningioma, no major side effects have been seen, and certainly, for that population as is true for breast cancer, one should not be inordinately concerned relevant to the use of this drug based upon the knowledge that we have.

Again, how does one balance side effects versus therapy. Etienne-Emile Baulieu speaks to the value of RU 486 in endometriosis. That is 10% of women who suffer pain, infertility and intestinal obstruction from this disease in the U.S. which can be associated with pelvic or abdominal fibrosis or adhesions. We have to cautiously study this drug under controlled conditions to see the balance of therapy versus toxicity.

The FDA position is a political one, because how could you oppose a drug and prevent it from getting into clinical trial by condemning it without evidence? There was an obvious political decision and not a scientific one, and it puts in question the rationality of the FDA's review. Who was responsible for this decision? What was the makeup of the Ru 486 review committee? Was Dr. Sobel of the endocrine branch of the FDA consulted or involved? The short term studies in abortion have an incredible safety record in 20,000 women. How can we know if the drug is toxic unless they let us test it?

2. Relevant to the alternative medical uses for this drug, there will be no excess commercial importation that violates the rules and regulations of the FDA. Any of the studies that we wanted to get started would have to begin under FDA auspices with IND approval following approval of Institutional Review Boards (IRB) at academic centers.

In relation to the possibility that RU 486 could get loose in the street as an abortifacient, this of course is only possible if abortion becomes an illegal act in the United States. As abortion is legal and is a federally acceptable procedure, why should Ru 486 become available as a drug smuggled in from alternative sources?

This fear is absolutely ridiculous when one considers the fact that there is major illegal use of narcotics, i.e., heroin and morphine derivatives in this country, and yet we do not stop providing patients available narcotics such as morphine, demoral, dilaudid, etc. for the treatment of pain. Is cancer any less worthy of treatment because someone might choose to use RU 486 illegally?

If one is that concerned with federal intervention, one can make RU 486 a controlled substance as we have done for narcotics. However, such a position is manifestly absurd when review of the literature in regard to RU 486 as an abortifacient or contragestational agent shows it to be far superior to current techniques that require direct instrumental intervention.

Opposition to RU 486 is quite obviously not based on any medical rationale, but is based upon an emotional attitude toward RU 486's physiologic action as an abortifacient or contraceptive.

Obviously, as long as abortion is legal, RU 486 will be available under prescription control by trained physicians as is true in France which will also be true in England and Sweden where it is being made available. The drug is ideally utilized in abortion in conjunction with a prostaglandin derivative, but if RU 486 were to also be developed as a contraceptive, the use of the prostaglandin would not be as critical. In the latter case, again we are dealing with an emotional issue as RU 486 blocks nidation and thus prevents the development of the fertilized egg. Is the fertilized egg, the equivalent of a fetus? The fertilized egg at the blastula stage that is associated with implantation is a mass of cells that has no human appearance.

I cannot see how commercial quantities of this drug can enter into the United States in violation of laws and/or pharmaceutical company controls in view of Food and Drug Administration controls and federal policing power. This drug is no different that any other drug regarding clinical study and should be available by prescription, if found useful for whatever use.

3. Mr. Benson is correct in regard to history of misuse of abortifacients. I am familiar with this during the period of time when abortion was illegal in this country. I clearly remember a nurse who accidentally killed herself by mistakenly using aminopterin (an anti-leukemia drug) as an abortifacient. It was a period of time when methotrexate, the related anti-cancer drug, was used to induce abortions by many women who managed to obtain it either illegally or as an excuse for the "treatment of psoriasis." It is of interest that many of our effective cancer chemotherapeutic agents are also abortifacients and might become available to patients if abortion is once more illegal. This of course is extremely dangerous, as

chemotherapeutic agents are infinitely more toxic than RU 486. If the reasoning of those who want to ban Ru 486 were to prevail, we would have to ban cancer chemotherapy because someone might use these drugs for abortion.

I have no idea why the FDA did not provide its physician surveillance requirement to RU 486, and instead embargoed the entire study of this drug for any use. Mr. Benson's concern for RU 486's safety in France as well as in this country are absurd, as we can control its use through FDA monitoring, which is standard for any drug in clinical research development.

Obviously, any physician would accept intelligent controls regarding the use of a drug that relate to honest concern for patients' welfare. Physicians are afraid of malpractice or peer condemnation and would not violate controls if they are rational. Controls that concern one portion of our population that looks upon abortion as a murderous act and thus introduces a moral issue as to whether a drug should be available should not enter into the medical evaluation of a drug. This is best seen regarding the retinoic anti-acne (Accutane) drug where, if misused during pregnancy, produce fetal malformation. Because some patients do not listen to doctors or misread labels should we condemn thousands of adolescents to facial scarring? The decision has been to permit its availability despite the fetotoxic effects if misused. RU 486 is not a fetotoxic teratogen. The pregnancy aborts, or if treatment is inadequate, normal fetal development can continue. **If the embargo on RU 486 continues, there will be no drug company exploration of other anti-progestin or anti-corticoid options for any medical use as drugs of this type could be used for abortion.**

4. In regard to its broader use in the treatment of a number of debilitating or life threatening diseases including breast cancer and hypertension, I enclose our commentary which appeared in JAMA.

Essentially, the references in our commentary document all that I have to say about the value of this drug in the treatment of cancer, and the complications of Cushing's disease which has a direct implication on many of the disease associated with the debility of aging. These include hypertension, adult onset diabetes, osteoporosis, immunodeficiency states, and stress related disease.

In addition, RU 486 may be an important factor in the control of obesity, as it prevents the development of corticosteroid obesity. As a progesterone antagonist, it should have potential for the treatment of physiologic obesity as women on massive doses of progesterone in the treatment of cancer put on up to 40 pounds of pure fat which theoretically can be prevented by the use of RU 486.

The potential for RU 486 in cancer is much broader than the positive results seen on phase I evaluation in breast cancer and in the treatment of inoperable meningioma. There are many tumors with corticosteroid receptors that are stimulated to grow by the presence of a corticosteroid in tissue culture or animal models. There are also tumors that are inhibited by corticosteroid action which might grow under the influence of RU 486, so that extensive, careful preclinical and clinical studies would have to be done to evaluate RU 486's place. The treatment of cancer by RU 486 might be governed by in vitro tissue culture studies, or sophisticated hormonal receptor analysis to provide the answer as to clinical response, but clinical testing in the final analysis has to be performed.

Most importantly, RU 486 has possible value in the treatment of AIDS. The Salt Lake City group has shown it to upregulate immunity in animal models. We made a major effort to get this off the ground in March of 1989 with Deeda Blair and E.E. Baulieu, attempting to contact the National Cancer Institute's David Broder in this regard. This ended when Hoechst AG's surrender to the "right to life" pressure eliminated the availability of the drug for any study, which of course was also followed by the FDA embargo.

In regard to quantifying the kind of positive results greater testing of RU 486 could have, I can only say that 43,000 of women with breast cancer die each year in the United States. Approximately 50% of these women are estrogen receptor positive which was the population tested at Montpelier. In the French study, 18% of these patients showed significant regression of disease at the terminal stage of their disease. I would guess that in advanced cancer, approximately 5,000 preterminal breast cancer patients each year could be helped by this drug, however, when used as an early adjuvant, it may be of prolonged greater value.

This drug is clearly the most effective drug we have in the treatment of Cushing's disease, but apart from its use in cancer, it deserves exploration in the treatment of malignant hypertension where we have shown it to have value in animal models, and in diseases of aging. Aging is very much like a Cushing's disease, and thus it may have a clear-cut place in the treatment of the debility of aging, which of course involves at least 25-30 million people above the age of 65.

Unfortunately I have not been able to test this drug in my own personal practice and would urge you to contact those individuals who have treated Cushing's disease and/or meningioma patients in this country for their clinical results. Please talk to George Chrousos at the NIH or Grunberg, et al. at USC.

7. In relation to our efforts to get a clinical study in advanced cancer patients off the ground, I met with Baulieu, Phillebert, and others at Roussel Uclaf in January of 1989. Our plan was to have a meeting in the U.S. which was eventually scheduled

for the first part of April with Larry Norton, M.D., who is the chief of Breast and GYN chemotherapy at Memorial Sloan Kettering. At that time, Dr. Norton was the chairman of the breast cancer committee of the CALGB cooperative study group which is supported by the National Cancer Institute. The plan was to meet to discuss a program that was to be supported by Roussel Uclaf to do a phase II study of RU 486 based upon the Montpelier 1987 study in advanced breast cancer. This meeting was canceled at the end of March.

In relation to a study in AIDS, we met with Deeda Blair, the assistant to Mary Lasker of the Lasker Foundation who had taken a proposal to test RU 486 prepared by our group for consideration in the treatment of AIDS to David Broder of the National Cancer Institute (of azidothymidine fame). For this purpose, we prepared a position paper which was given to Deeda Blair and E.E. Baulieu as part of a preliminary meeting that was to have taken place in March to have developed NCI, NIH support in studying this drug. This died when it came apparent that the drug would not be available in this country.

My own experience in trying to get RU 486 available, was originally focussed on its potential use in the treatment of advanced breast cancer patients, and for its potential value in the treatment in syndromes associated with aging (i.e. the Cushing's syndrome model). My first attempt to interest Roussel-Uclaf in working with us were begun in September of 1988 in anticipation of my going to Paris for a meeting sponsored by Roussel-Uclaf dealing with a hormone of interest to my own research. We were turned down initially but with encouragement within the Roussel-Uclaf organization, I contacted Dr. Sakiz, the director of Roussel-Uclaf and he revised his negative position to one of positive support. Meetings were held in January at the Paris hormone conference and all seemed to be positive in regard to moving ahead. With Dr. Kalimi, we also presented data for its value in malignant hypertension. What killed Roussel-Uclaf's participation appeared to be the action of Hoechst AG which was threatened by "right-to-lifers" with an international boycott if they allowed RU 486 to develop beyond the two countries it was already being used in, i.e. France and China. It is my understanding in talking to people off the record at Roussel-Uclaf that it was Hoechst AG that prevented Roussel-Uclaf from going ahead (no one would speak for the record). Again, off the record, I talked to a representative of Hoechst AG who indicated that the company's position was a political one related to the economic pressures, i.e. the threat of boycott.

Right now, RU 486 is being legalized for use in abortion in England and in Sweden. It is of interest that a Swedish breast cancer study with RU 486 is being launched. My understanding now is that Roussel-Uclaf has a policy that it will only make RU 486 available to a country that accepts RU 486 as an abortifacient. This position of Roussel-Uclaf now puts all of us who want RU 486 for medical application for our patients in the position of having to support its use in abortion whether we would agree with its place there

or not. I think it very unethical of Roussel-Uclaf to make this an issue tied to abortion. Again, it is a question of ethical balance as the abortion issue has nothing to do with the medical place for RU 486, but it is a clever maneuver on Roussel-Uclaf's part to mobilize cancer patients, AIDS victims, hypertensives, diabetics, osteoporotics (the aged) and the obese in support of RU 486 for abortion.

RU 486 should be better ethically used to prevent pregnancy rather than to abort a living fetus. Its use as a contragestational agent prevents the egg in the womb before it will become a fetus. However,it is my feeling that as long as abortion is legal, RU 486 should be available for this purpose, and should be also available for medical use. If abortion once more becomes illegal, then RU 486 could be made available for medical uses under controlled medical license by prescription with appropriate state and/or federal controls as if it were a narcotic. I would be against this, but if it obtains this drug for my patients, we should accept it.

It is apparent that if we are going to have state by state abortion approval or disapproval following a "pro-life" Supreme Court decision, then each state will have to develop its own interface with Roussel-Uclaf for the clinical medical development of RU 486. This raises a major question as to whether or not we can retain federal controls wherein the FDA can, by force, control drug availability in this country for "pro-life" reasons. Will the FDA be able to develop a dual policy of non-restriction for states that permit RU 486 in abortion and for states that do not? Will this cause a new civil war, bloodier than the current "freedom of choice" - "right to life" fight. Will RU 486 be taken over by a Medallin Columbia cartel that will sell it on street corners? The legal, social, and political ramifications of this kind of situation are too much for me to understand, as I see the issue as one of ethical balance between the value of the lives of 43,000 women dying of breast cancer versus the survival of an unwanted fertilized egg.

Sincerely yours,

William Regelson, M.D.
Professor of Medicine

WR/e

Testimony of

Kathryn B. Horwitz, Ph.D.*

Small Business Subcommittee on
Regulation, Business Opportunities and Energy

Monday, November 19, 1990

*Vitae appended

Chairman Wyden, Committee Members, Ladies and Gentlemen:

My name is Kathryn (Kate) Horwitz. I hold a doctorate degree in Molecular Endocrinology, and am Professor of Medicine, Pathology and Molecular Biology at the University of Colorado School of Medicine.

I am here today because I study the actions of sex hormones in cancer.

Breast cancer: As you may know, 1 in 9 American women will develop breast cancer in her lifetime. This compares to 1 in 1000 American men. Why do mostly women develop breast cancer? It is not because women have breasts as you might think; it is because they have ovaries. A woman whose ovaries are removed at an early age develops breast cancer at the same rate as do men. What then, is it about her ovaries that sensitizes a woman to developing breast cancer? The cause appears to be the two major female sex hormones produced by the ovary -- the hormones called estrogen and progesterone. These two hormones regulate the growth and function of the uterus and breast during the normal menstrual cycle. Unfortunately, the same two hormones also regulate the growth of cancers in these two organs. While extensive research continues in this area, it appears that, especially in the breast, both hormones stimulate the growth of cancers.

That's the bad news. The good news is that this gives doctors a way to arrest breast cancer growth. It seems intuitively obvious that if estrogen is a growth promoter, then treatment with an antiestrogen should shrink the tumors. This is, in fact, the case, and drugs that are antiestrogens are a major way in which breast cancers are treated. The main antiestrogenic drug is called tamoxifen; it has been available for at least 20 years; and it is in routine clinical use.

Now, how would you treat the fraction of breast cancer cells that are stimulated to grow by progesterone? Clearly, you would use antiprogesterone therapy. As you all know, only one antiprogestin drug exists today -- it is called RU486.

Let me point out another property of breast cancers. While the tumors of some women will shrink under first-line treatment with the antiestrogen tamoxifen, eventually the tumors become tamoxifen-resistant, and regrow. At this point, second-line treatment with an antiprogestin, should lead to a second remission of the breast cancer. A preliminary clinical trial using RU486 to demonstrate this point, has been reported by a French research group. They found that RU486 halted cancer growth to some extent in 12 of 22 breast cancer patients, after all other treatments, including tamoxifen, were tried and failed! RU486 was found to be safe and well tolerated. Furthermore, it had an additional important, but unanticipated effect,

Apparently, RU486 was analgesic -- it freed women from pain due to metastasis of cancer cells to the bones, which allowed them to be withdrawn from other painkillers, like morphine.

In the U.S. approximately 150,000 new cases of breast cancers will be diagnosed this year, and 1/3 of these, approximately 50,000, are hormone dependent and candidates for hormone antagonist treatment. Tens of thousands of women whose cancers are not new also require these kinds of therapy.

Meningioma: But breast cancer is not the only cancer that can be treated by antiprogestins. Meningiomas are brain cancers that affect both men and women. In women they may be exacerbated by pregnancy, and improve after delivery, in parallel with the rise and fall of progesterone. These cancers have an unusual but tantalizing hormonal property -- they contain high levels of receptors for progesterone but not for estrogens. Receptors are the molecular targets of sex hormones within the cell -- estrogen receptors bind estrogens or the antiestrogen tamoxifen; and then turn on growth controlling genes. Progesterone receptors bind progesterone and RU486, and regulate other growth controlling genes. The fact that meningiomas contain mainly progesterone receptors suggests that in both men and women, progesterone is driving the growth of these cancers and that antiprogestin therapy should shrink the tumors. Again, clinical trials using RU486 for meningioma treatment are underway in France and England to confirm this.

It might interest you to know that a meningioma patient from North Carolina is at present in England undergoing RU486 treatment for her brain cancer, because her doctor in North Carolina could not obtain the drug.

Basic Research: The hormone receptors I just mentioned are the way by which the sex hormones communicate with the cell. Understanding how receptors act is a major area of basic research. These experiments require use of both the hormone and its antagonist. If, with a hormone antagonist, you can stop something specific from happening, it gives you important clues about the normal actions of that hormone. At present, RU486 is the only progesterone antagonist available for studies to help us unravel how progesterone is involved in the development, growth and treatment of progesterone-controlled cancers.

Prostate Enlargement and Prostate Cancer: The problem before you today touches not only on women's cancers and women's issues. Many men suffer from prostate enlargement and prostate cancer. This abnormal growth of prostatic tissues in men is driven by the male sex hormone -- testosterone. Like estradiol and progesterone, testosterone acts through the testosterone (or androgen) receptor. Prostate enlargement and prostate cancers are treated with testosterone antagonists, or antiandrogens. (The alternative treatment, namely castration, is not not very popular with men). The point I wish to make is that what we learn experimentally about antiprogestins, like RU486, has a

direct impact on what we understand about antiandrogens, and will help us to design better drugs for prostate cancer treatment as well.

RU486 - Non Cancer Uses: RU486 has additional uses besides cancer treatment and as a research tool. There are many reasons to think that RU486 may be important in treatment of endometriosis; in treatment of premenstrual syndrome; for menopausal symptoms; to trigger labor in cases of undue delay; to facilitate post-partum milk production. I cannot emphasize too strongly the powerful clinical and experimental potential of antiprogestins. Scientists have sought such drugs for at least 20 years.

The FDA Import Alert: The FDA's restriction on RU486 import states as its rationale that the drug "could pose a risk to the safety of the user". This is untrue. European studies involving more than 50,000 women show that the drug is safe and effective when used as prescribed and under a doctor's supervision. Thousands of drugs currently in use in the United States have the same provisions.

How the FDA arrived at its conclusions regarding safety is not clear. I have called several of America's leading experts on antiprogestins in breast cancer and reproduction to ask them whether the FDA solicited their advice about RU486. None of these physicians and scientists were consulted by the FDA (a list is appended).

... Enforcement of the import alert means that thousands of men and women are denied access to a safe and critically important drug to treat not only cancers, but to correct many other hormonal problems.

... Enforcement of the import alert means that I no longer can obtain RU486 for basic research of progesterone receptor action in breast cancer, or for studies of the mechanisms of action of sex hormone antagonists.

... Enforcement of the import alert is an insult to patients, to their physicians, and to scientists. It argues that because it has potential for abuse, tens of thousands of patients should be denied its legitimate use.

It is not clear why the FDA singles out this drug from among hundreds of drugs that <u>are</u> approved for legitimate uses, despite their potential for abuse.

Thank you.

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APPENDIX

The following American experts on RU486 and progesterone action were not consulted by the FDA prior to issuance of the import alert:

BW O'Malley, M.D.

Professor and Chairman,

Cell Biology Department,

Baylor College of Medicine,

Houston, TX.

WL McGuire, M.D.

Professor and Head of Oncology,

Editor: "Breast Cancer Research and Treatment",

University of Texas Health Science Center at San Antonio,

San Antonio, TX.

Marc Lippman, M.D.

Professor and Head,

Vincent T. Lombardi Cancer Center,

Georgetown University School of Medicine,

Washington, DC.

Benita Katzenellenbogen, Ph.D.

Professor of Physiology/Biophysics,

University of Illinois,

Urbana, IL.

Gary Hodgen, Ph.D.

Professor,

Jones Institute for Reproductive Medicine,

Eastern Virginia Medical School,

Norfolk, VA

Wayne Bardin, M.D.

Professor and Director,

Center for Biomedical Research

The Population Council

New York, NY

STATEMENT BY

GEORGE P. CHROUSOS, M.D.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

OF THE

NATIONAL INSTITUTES OF HEALTH

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES AND ENERGY

OF THE

COMMITTEE ON SMALL BUSINESS

U.S. HOUSE OF REPRESENTATIVES

November 19, 1990

Mr. Chairman, and Members of the Subcommittee:

My name is Dr. George Chrousos and I am a senior investigator and Chief of the Section on Pediatric Endocrinology in the National Institute of Child Health and Human Development at the National Institutes of Health (NIH) in Bethesda, Maryland. I am pleased to have this opportunity to tell you about my research with the drug RU 486.

I have been with the NIH Staff for over twelve years and for an equal number of years I have worked on the development of pharmacologic agents which work against the negative effects caused by too much of the natural hormones glucocorticoids. Because RU 486 does work this way, I have been conducting research with this drug for a number of years. The focus of my work has been to develop new diagnostic procedures and treatments for Cushing's Syndrome, a serious, and sometimes fatal, condition caused by an excess of glucocorticoids, and to further our understanding of the role of glucocorticoids in health and disease. RU 486, which binds to the glucocorticoid receptor and prevents the hormone from exerting its effects, provides an excellent means of accomplishing these goals.

Cortisol is a natural glucocorticoid hormone in man. Though this hormone is necessary for life, when it is secreted in excess it has profound adverse effects on the health of the afflicted individual. These effects include excessive weight gain, severe

weakness, mental depression, osteoporosis (thinning of the bones), development of diabetes mellitus, hypertension, atherosclerosis, and suppression of the immune system. The syndrome is fatal, if left untreated. Cushing's Syndrome occurs in both sexes and in children and adults alike. The majority of those afflicted with this disorder, however, are women in their third and fourth decades of life.

Spontaneous Cushing's Syndrome is not a common affliction. The form of spontaneous, severe disease that we treat at the NIH affects between 250 and 1,000 new patients in the United States every year. As a result, however, of the widespread use of pharmacological doses of glucocorticoids administered for therapy of a wide range of diseases, millions of people suffer from a mild variant of this condition.

Spontaneous Cushing's Syndrome is caused by tumors of the adrenal glands that secrete cortisol, or tumors that secrete another hormone called ACTH, which stimulates cortisol secretion by the adrenal glands. ACTH can be produced either by tumors of the pituitary gland or by tumors elsewhere in other organs, such as the lungs, the thymus, or the pancreas. Because these organs do not normally secrete ACTH, the Cushing's Syndrome that results from such abnormal secretion of ACTH is called ectopic ACTH syndrome.

Since 1983, we have performed research at the NIH on the therapeutic use of RU 486 in a subgroup of patients with Cushing's Syndrome. These patients were selected from a pool of individuals with Cushing's Syndrome referred to the NIH for diagnosis and treatment. They had either the ectopic ACTH syndrome, or an adrenal tumor secreting cortisol. Their tumor was either inoperable, because of widespread metastatic disease or could not be located by all available diagnostic procedures at the time of initiation of therapy. All patients were gravely ill at the time that the decision was made to administer the RU 486 therapy. The medication was given to them orally, in accordance with an NIH-approved protocol and an Investigational New Drug application approved by the FDA for this clinical trial. We saw positive responses in our patients approximately two weeks after the therapy was begun, with amelioration and gradual disappearance of Cushing's Syndrome symptoms and signs.

The first patient treated with this medication was a 25-year-old man with a lung tumor which had already spread to the bone marrow. This patient, with full-blown Cushing's Syndrome, due to ectopic ACTH secretion by the tumor, had a severe form of depression and had attempted suicide prior to admission at the NIH. Before we started seeing physical changes in the condition of this patient, his mental depression was lifted in a spectacular manner with the medication. He had a nine week course of therapy--because of limited supplies of the drug at

that time--with complete reversal of the syndrome, including elimination of his diabetes mellitus and correction of his hypertension. At the conclusion of the therapy, he underwent major surgery to remove both of his adrenal glands with no complications. Such surgery in untreated and unprepared patients with Cushing's Syndrome has a very high incidence of severe morbidity or mortality.

Another patient, a 43-year-old man with an ACTH secreting tumor which could not be located, was treated with RU 486 for almost a year with excellent results. At that time, a lung tumor was diagnosed and was removed surgically. The patient's major surgery was uncomplicated and he was cured for life. RU 486, thus, allowed both interim care until the tumor could be located, and prepared the patient's tissues to successfully withstand the necessary major surgery.

Overall, eight patients with Cushing's Syndrome were treated with RU 486 for periods of four weeks or longer. The clinical response was excellent in five patients and the improvement was sustained for as long as treatment with this medication was continued. Complete regression of the features of the disease was observed in all of these patients. The two patients treated for the longest periods were given the drug for 11 and 22 months, respectively.

The toxicity of the treatment with RU 486 included treatable nausea in three patients and mild enlargement of breast tissue in two male patients. Two patients developed adrenal insufficiency on RU 486, which, however, subsided with appropriate therapy. The adrenal insufficiency was a result of administration of the drug in doses found to be too large, and decrease of the dosage was associated with elimination of this side effect.

In summary, RU 486 therapy was successful in over 50% of the Cushing's Syndrome patients to whom it was administered. Its efficacy was 100% in 5 of 8 patients, who showed an excellent response. The side effects observed with RU 486 were mild or of a transient nature. Appropriate individualization of the dose to achieve the optimal response to the medication, and regular monitoring of the patients on RU 486 therapy is recommended, however, because of the potential of this medication to cause adrenal insufficiency. The patients given RU 486 should be taught to recognize the potential onset of adrenal insufficiency and how to treat themselves with glucocorticoids. A parallel situation is the self-treatment with insulin of diabetics in whom the dosage of insulin has been carefully individualized to avoid either over- or undertreatment.

According to our estimation, a small but significant number of patients with spontaneous Cushing's Syndrome would benefit from RU 486 therapy each year. Mitigation of symptoms and improvement

of the quality of life, as well as outright saving of life, would be expected for these patients.

In the course of our research with RU 486 and Cushing's Syndrome, other important research issues involving this drug have become apparent. Given the profound roles that glucocorticoids play in development, brain function, metabolism, stress physiology, and immune system functions, the scientific questions that can be asked with RU 486, an excellent probe of glucocorticoid action, are of major importance and should be pursued.

STATEMENT BY

LYNNETTE K. NIEMAN, M.D.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

OF THE

NATIONAL INSTITUTES OF HEALTH

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES AND ENERGY

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November 19, 1990

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here this morning to testify regarding research on RU 486. My name is Lynnette Nieman. I am a board-certified physician in the fields of Internal Medicine and Endocrinology and Metabolism. Since 1983, my colleagues and I have used RU 486 in clinical studies as members of the Developmental Endocrinology Branch of the National Institute of Child Health and Human Development at the National Institutes of Health. I will review for you our published studies regarding the potential use of RU 486 as a contraceptive agent, and I will comment on the usefulness of the compound in the investigation of normal female physiology and infertility.

Because it blocks the action of the hormone progesterone, RU 486 is a compound that has great potential to aid in our understanding of normal female physiology, and to provide new approaches to a variety of conditions related to female reproduction. To understand the excitement engendered by the recent availability of this antiprogestin compound, one must review the menstrual cycle and the role of progesterone in the reproductive function of women. The cycle begins on the first day of menstruation and leads to a pregnancy or ends on the day prior to the next menses. During the first half of the menstrual cycle an egg matures in one of the ovaries, surrounded by cells that make the hormone estrogen. Estrogen causes the uterus to rebuild its lining, or endometrium. This half of the cycle is called the follicular phase, in reference to the maturation

of the egg-containing follicle. The follicular phase ends when the fully-developed egg is released from the ovary in a process called ovulation.

After ovulation the hormone-producing cells which previously surrounded the developing egg form a new structure called the corpus luteum, whose function is to secrete both estrogen and progesterone. Progesterone causes the uterine lining to make and secrete new compounds and to develop further in preparation for a possible pregnancy. After ovulation, the egg travels through the fallopian tube towards the uterus. Fertilization of the egg by a spermatozoa may occur during this journey. If this occurs, the fertilized egg develops into a ball of cells called the blastocyst, which attaches to the uterine lining and begins to implant around 6 - 7 days after ovulation. If both the process of implantation and embryonic development progress normally, a hormone called human chorionic gonadotropin, or hCG, is produced and reaches the maternal blood. This hormone stimulates the corpus luteum to continue making estrogen and progesterone, which are needed for the continued integrity of the endometrium. If the corpus luteum is not "rescued" by hCG, it stops making these steroids and disappears. As a result, the endometrium falls apart because of the loss of progesterone support, and the cycle ends as the uterine lining is shed and menses begins. The second half of the cycle is referred to as the luteal phase, in recognition of the importance of the corpus luteum. Thus, progesterone is produced in the luteal phase, and functions to prepare the endometrium for implantation and pregnancy, and to

support the endometrium during pregnancy. It is known that low levels of progesterone are associated with infertility and repeated miscarriage, demonstrating the importance of this hormone.

RU 486 has a structure similar to that of progesterone. Like progesterone, it interacts with the cellular machinery, called receptors, that initiate the effects of progesterone; unlike progesterone, RU 486 does not activate the receptors, and no progesterone effects result from its interaction with the receptor. When both RU 486 and progesterone are present they compete with each other to interact with the receptors, and in this way RU 486 blocks the action of progesterone. The essential role of progesterone in the preparation of the endometrium for pregnancy led us to speculate that blockade of its action would prevent the establishment of pregnancy. We have explored this hypothesis in our studies of the potential contraceptive properties of RU 486. Development of new contraceptive strategies refers to methods that would act before there is an established pregnancy.

Our studies of the contraceptive potential of RU 486 have three parts. First, we explore, in women, a physiologic effect of RU 486 that may have contraceptive properties; second, we determine, in a laboratory animal, the contraceptive efficacy of the agent when given in the same way; and third, we evaluate the toxicity of the agent in women and animals. The women who participate in our studies use non-hormonal methods of birth control during the studies and are excluded from study if they are pregnant. Thus we have not

performed a contraceptive trial of RU 486 in which the compound is given to women who may become pregnant; rather, we infer contraceptive potential from the human studies, and test it in the animal studies.

Our first study, "The progesterone antagonist RU 486: a potential contraceptive agent", was published in the New England Journal of Medicine in 1987 (Vol. 316, pp 187-191). In this study we tested the hypothesis that administration of RU 486 in the mid-luteal phase would interrupt the progesterone support of the endometrium and have a contraceptive effect. Women received RU 486, at a single 10 mg/kg body weight dose, on the seventh luteal phase day. RU 486 consistently induced vaginal bleeding within 72 hours. This suggested that giving a single dose of RU 486 late in the cycle might be an effective contraceptive strategy. To test this, female rhesus monkeys mated during each cycle were given a single dose of RU 486 (5 mg/kg) or a placebo on day 25 of the cycle. None of the animals receiving RU 486 became pregnant, while the placebo-treated group had a 28% pregnancy rate. No untoward side-effects were noted in women and no toxicity was seen in the monkeys. These data suggested that RU 486 has the potential to function as a contraceptive agent when given in this way.

This study represented only one of many contraceptive strategies that could be explored using RU 486. For example, we and others have shown that ovulation can be delayed or prevented completely by follicular phase administration of RU 486. The way in which the

compound does this is not entirely clear. The hormonal signal that causes ovulation is blocked by RU 486; the compound may also affect the development of the egg. These effects could be further exploited for contraceptive potential. Since progesterone is important during the entire luteal phase, numerous other regimens of RU 486 administration could be devised to further explore its ability to prevent pregnancy.

RU 486 is very interesting in that its effects are both dose- and time-dependent. For example, when given in the follicular phase, when no progesterone is present, RU 486 does not cause menses, regardless of the dose. When given in the luteal phase in increasing doses, menses is the first effect. At higher doses RU 486 also decreases progesterone secretion. Similarly, the effects on ovulation depend on the dose of RU 486 and the number of days in which it is given. Thus, one cannot refer to RU 486 as a "menses inducer" or "ovulation blocker" without stating the time of the cycle and the way in which RU 486 is given.

One important area of inquiry in all clinical investigation is the safety of a new compound. The untoward side-effects of RU 486, like its other actions, are dose-dependent. We have seen no adverse effects at single doses of up to 25 mg/kg body weight, or daily doses of 3-4 mg/kg body weight given for four days. One potentially life-threatening toxicity, complete blockade of cortisol action, has not been seen in normal individuals, as they respond to RU 486 (single doses up to 25 mg/kg body weight) by increasing the amount of

ACTH, the hormone that stimulates cortisol production. In this way more cortisol is available and the RU 486-induced blockade of its action is prevented. The toxic side-effects that have been observed have been seen at doses of 10 mg/kg body weight or greater, given for more than one week. My colleague, Dr. Chrousos, addresses this issue in his discussion of the use of RU 486 in the treatment of Cushing's syndrome.

In summary, RU 486 is a chameleon of sorts, with a variety of effects that depend on the system being examined, and the dose and frequency with which the compound is given. With regards to the reproductive system in women, there remain many physiologic questions regarding the role of progesterone that could be probed using this antiprogestin drug. The studies to date have suggested that RU 486 may have unanticipated effects (such as inhibition of follicular development), that may illuminate previously unasked questions. Further studies of RU 486 will certainly help us to understand better the normal reproductive physiology of women. By mimicking conditions of progesterone deficiency we hope to enhance our understanding of these conditions and expand the diagnostic and therapeutic approaches to women to are involuntarily infertile. RU 486 holds promise of providing both greater insight into infertility and new contraceptive strategies.

STATEMENT OF MRS. WANDA GUESNIER
BEFORE THE SMALL BUSINESS SUBCOMMITTEE ON
REGULATION, BUSINESS OPPORTUNITIES AND ENERGY

NOVEMBER 19, 1990

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CHAIRMAN WYDEN:

Thank you for inviting me here this morning to testify about my experience with Cushing's Syndrome and the use of the Drug RU 486.

My Name is Wanda Guesnier. I am a 57 year old secretary and mother of 3 from Lubbock Texas. I am in Washington this week for treatments at the National Institutes of Health as part of my on-going battle against Cushing's Syndrome.

Cushing's Syndrome is a hormonal disorder caused by prolonged exposure of the body's tissues to high levels of cortisol. It generally results from a tumor of (1) the pituitary gland; (2) the adrenal glands; or, (3) ectopic tumors found in any part of the body. Approximately 10 people in every million are affected by the disease.

I first became ill in December, 1986. I was tired all of the time and I experienced a un-accountable weight-gain (approximately 20 pounds). At first, I attributed it to my age and continued on with my life. However, as time passed, I began experiencing symptoms that made me aware that something might be seriously wrong.

I began to experience hypertension, muscle weakness, excess hair growth, moon face, a loss of memory, extreme mood swings and I was often disoriented. I contacted a doctor of internal medicine and underwent extensive testing. He told me that I had an "extra loop" in my colon and that I should go home and exercise.

By May, 1987, my symptoms seemed to go into remission -- the swelling went down and I returned to normal. In January of 1988, however, all of the symptoms returned. I contacted an oncologist who did another thorough examination. She recognized that I had the classic symptoms of Cushing's syndrome. She recognized the disease from her training at the National Institutes of Health (NIH).

I was admitted to a local hospital for an additional week of testing. I was told that normal cortisol levels run at about 90. Mine were over 9000. My doctor immediately contacted NIH and arranged for NIH specialists to examine me as soon as possible.

Within two weeks, I had deteriorated to the point where I could no longer function. I felt that the end was very near. My Doctor again called NIH and I was admitted within the week.

I underwent 6 weeks of testing at NIH beginning in February,1988. I was advised that my tumor was ectopic. Such tumors can be very small, sometimes only the size of a head of a pin, and the doctors couldn't locate my tumor. They gave me three treatment options to help lessen my symptoms. One of these options included treatment with the experimental drug RU 486. After carefully considering side-effects and my prognosis, I chose to try RU 486.

A week after I first started taking the drug, the feeling came back into my arms and legs, the swelling went down, my blood pressure returned to normal, and my mind was clear. For the first time in months, I felt like I was on the way to feeling "normal" again. I was released in April, 1988, and returned home. At the time, I was taking 300mg of RU 486 twice a day.

In August, 1988, I returned to NIH where I underwent surgery to remove the lower lobe of my left lung where a tumor of the type that causes Cushing's Syndrome had been found. Unfortunately, this did not fully clear me of the disease, and I underwent a second chest surgery in January of 1989 to remove all the nodes in the ares of the original tumor, my chest and neck. In AUgust 1989, a spot was found by MRI on the back of my left lung and I underwent a third surgery.

At this time, Dr. Cutler, the head endocrinologist at NIH, discussed with me the possibility of removing my adrenal glands in the hope that I could return to a normal life. In preparation for this operation, my dosage of RU 486 was lowered to 200mg, twice a day, with a total abstinence from the drug in the two weeks prior to my last surgery.

Since that time, I have been able to return to my normal life. However, they are still searching for the tumor(s) which caused the disease and which may or may not be malignant.

I used RU 486 for 20 months with no apparent side effects. I felt extremely well during the period I used the drug and my symptoms were effectively blocked. If RU 486 can block cortisol so effectively without any side effects, surely additional research will find other equally rewarding uses for the drug. We shouldn't automatically close our minds to this drug because it can also be used as an abortifacient.

Please don't close the door to further research with this drug or close your hearts to the possibility of giving hope to thousands of Cushing Syndrome victims seeking a cure to this terrible disease.

Thank you again for the opportunity to testify this morning. I will try to answer any questions you may have.

STATEMENT OF JAMES F. NELSON
BEFORE THE SMALL BUSINESS SUBCOMMITTEE ON
REGULATION, BUSINESS OPPORTUNITIES AND ENERGY

NOVEMBER 19, 1990

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MR. CHAIRMAN:

I want to thank you for this opportunity to testify before this subcommittee regarding Cushing's Syndrome and the drug RU 486. My name is James F. Nelson. I am 47 years old, married with four children, and I live in Flemington, New Jersey where I work as a plant foreman for a plastics dispersion company.

I am here this morning to talk about my experience with Cushing's Syndrome and RU 486.

I was first diagnosed with Cushing's Syndrome in 19 . At first, I didn't think that my symptoms were all that serious. However, I soon began experiencing increasingly painful problems. My symptoms included severe mood swings, unaccountable weight gains, swollen tissue about my face and neck, hair loss, bladder difficulties, the loss of muscle and muscular weakness.

Obviously, these physical symptoms made it difficult, if not impossible, both to do my job and to live a normal life. As the symptoms increased, more and more of my time was being taken up medical appointments, blood tests, urine tests, CAT scans and X-Rays -- all looking for the source of the disease.

I began treatments for Cushing's Syndrome at the National Institutes of Health (NIH) in March of 1986. It was at this time that I began an experimental course of treatment with the drug RU 486. Researchers had been using several other drugs to treat

Cushing's Syndrome, but they told me that they had very positive results with RU 486. Under the therapy program, I was taking dosages of the drug 4 times a day.

Within a month or two of beginning treatments with RU 486, many of the symptoms that I suffered from began to clear up. My problems with high blood pressure and hypertension lessened, my mood swings became less dramatic and my bladder problems eased. In fact, after a few months of treatments with RU 486 all of the symptoms of Cushing Syndrome disappeared. The moon face, hair loss, swelling, the hump on the back of my neck all went away. In short, the disease went into remission.

In all, I was treated with RU 486 for about one year. I feel that the treatments were very successful. I only experienced minimal side effects, such as beast enlargement. After a long, painful period where any kind of activity was difficult, I was actually able to return to some semblance of a normal life.

Having gone through this experience, I feel that RU 486 made a definite difference in helping me fight this disease and in saving my life.

RU 486 gave the NIH doctors and staff the time that they needed to find the tumor that was causing my Cushing's Syndrome. Eventfully, the doctors found and removed the tumor. Without RU 486, I'm not sure that I would have been strong or healthy enough to survive that surgery.

I feel very fortunate that I was able to be part of the project testing RU 486 and that the treatment was so successful. I hope that research into the practical uses of this drug will continue, and I also hope that other Cushing's Syndrome sufferers will have the same opportunities that I had.

Thank you for this allowing me the chance to speak with you this morning and I will be happy to answer any questions you might have.

STATEMENT OF ANDREA HECHT, PRESIDENT,
NATIONAL CUSHING'S ASSOCIATION

Mr. Chairman, and the other honorable members of the Small Business Subcommittee on Regulation, Business Opportunities and Energy, thank you so much for the opportunity to testify before you today on the restrictions and barriers to the use, marketing and testing of RU486 in the United States. As the president of the National Cushing's Association (NCA), I am representing the interests of our patients, our physician experts - both endocrinologists and neurosurgeons - and the family members of those affected by this devastating and rare endocrine disorder. The NCA is a non-profit patient education and support organization which I started, with two other Cushing's patients, approximately three years ago. Our goals at that time were the same as they are today -

1) to provide accurate medical information to patients and physicians, regarding Cushing's disease/syndrome
2) to provide understanding and support, in any way possible, to Cushing's patients and their families
3) to help educate both the medical community and the lay public about this endocrine disorder
4) to encourage more clinical research into the origin of and the new treatments for Cushing's disease/syndrome

At the time I helped start the NCA several years ago, I was a patient myself, recovering from a two-week hospital stay after a pituatary surgery known as transphenoidal surgery. This surgery came more than 12 years after I was certain my Cushing's had been corrected at a major teaching hospital in Southern California. Like many patients, however, I discovered that my

doctors were not as informed on this rare disease as they might have been and they also did not seek out the most current clinical treatments on my behalf. In short, they removed my healthy adrenal glands instead of my pituatary gland, in which a benign tumor was growing - and continued to grow for 12 long years.

While I was recovering I was fortunate to meet another Cushing's patient and the initial root of the NCA began to grow. Over the past years, we have worked very hard to both reach out to patients who are suffering currently, as well as those who have suffered in the past. There is absolutely no cure for Cushing's at this time so patients have to learn to accept uncertainity about their medical futures, while making peace with their past. It is important for you to know that from the NCA's experience, most patients are not diagnosed correctly for about three years. In addition, it is not unusual for our patients to experience a seven or eight year delay from onset of the illness/symptoms and a correct diagnosis. Needless to say, upon appropriate treatment, patients bear a great many emotional scars throughout their recovery from Cushing's. This is not an easy disease for patients to deal with.

Let me offer you some typical remarks which we hear regularly at the NCA. This is a patient who was diagnosed six years ago and was ill for quite some time before a doctor recognized her symptoms.

> "I saw more doctors than I can remember, was given many drugs, most of them anti-depressants. The doctors were

convinced that I was suffering from too much stress and of course, hypochondria. I spent thousands on counseling which did me no good. Finally a doctor told me that my job was probably the cause of my "stress". So, I quit my job and of course lost my health insurance benefits with it. I was by that time too ill to work anyway. I was diagnosed, had a tumor removed and was placed on replacement therapy drugs. It's been five and a half years now since my last surgery. I am still unable to resume a normal lifestyle. I thought that maybe after surgery and of course about $30 thousand dollars in unpaid medical bills I would be alright. If I had known what life would be like, I never would have gone through the surgery. Sometimes I don't think I can go on like this."

As you can see, Cushing's is more than just an illness which gets diagnosed and then treated. The scars left behind from Cushing's are deep, permanent and tender. On behalf of the more than 20,000 past patients in the U.S. today and the thousands more yet to come, I sit before you today to discuss the medical need for RU486 - possibly a beneficial treatment for an unknown amount of Cushing's patients.

To discuss the need for RU486, let me first explain Cushing's to you. Cushing's is an endocrine disorder, affecting mostly women in their 20's-40's, in which the body begins to overproduce - in massive amounts - cortisol, via the adrenal glands. This process is overseen by the pituatary gland, located

in between the optic nerves. The pituatary gland, in normal people, sends out messages to the adrenal glands signaling when and how much cortisol is needed by the body. For example, if you have the flu, the pituatary automatically signals the need for more cortisol because of the stress the body is under in fighting the flu. In Cushing's patients, the system still works - in fact, it over works to the detriment of the patient. The signal from the pituatary to the adrenal glands does not shut off - thus continuing to send false messages in regard to the body's need for additional cortisol. These messages from the pituatary are called receptors, and in the case of Cushing's, the receptors are working overtime. Some of the symptoms that result because of this failed system include:

loss of menstrual periods
high blood pressure
extreme muscle weakness
osteoporosis or brittle/broken bones
acne
facial hair growth in women
unusual weight gain, in the trunk only
easy bruising
purple stretch marks
depression

Cushing's can originate in one of three locations in the body. By far, more than half of all Cushing's is pituatary in origin. Usually a very small, benign tumor known as microadenoma, is discovered on the anterior pituatary gland. In

some cases, a benign tumor is discovered on one of the adrenal glands. And most rare of all, is ectopic Cushing's in which a cancerous tumor, often in the lung but certainly in another part of the body, is causing the problem. Traditional treatments to date include removal of the pituatary adenoma by a specialized neurosurgical procedure known as transphenoidal surgery, or removal of the affected adrenal gland. For many patients, these treatments relieve the predominent symptoms and reverse the process. For some, these treatments simply do not work. It is for those patients that the NCA urges you do everything you can to encourage the study of RU486 in treating Cushing's.

As a patient advocacy organization, we believe the medical literature indicates that RU486 presents promise for a portion of tomorrow's Cushing's patients. There is no way for us to know how many people that might be because at the present time, there is no accurate data base from which we might extrapolate future numbers of patients.

But what we do know is this. RU486 is a potent glucocorticoid receptor blocker. That means the drug effectively stops cortisol from acting. For Cushing's patients, this drug could prove to be one more step toward achieving a happy, healthy life once again. The NCA does not want to see those steps blocked because politics has intertwined its issues into the progress of science. As Dr. Richard Horton, Chief of the Division of Endocrinology and Metabolism and a national researcher and expert on Cushing's has said:

"In Cushing's syndrome, RU486 could potentially block

> the aciton of cortisol and thus reverse and control the disease . . . I certainly favor the availability of this drug from the French Manufacturer for use as an investigational tool in order to find its proper use in Cushing's syndrome . . ."

The NCA agrees with Dr. Horton's position - that RU486 should be made available for Cushing's patients to use, when necessary. In response to acting FDA Commissioner James Benson's remarks that RU486 posed unacceptable safety risks to the American public, we offer the following information. Of the thousands of Cushing's patients who the NCA has spoken to and or heard from over the past years, every single one has supported not only the need for effective drug therapy - even drug therapy with risks - over the option of the surgical procedure and the risks, and costs which accompany that option. We recognize that RU486 may not be the answer for all Cushing's patients, but for those who it will help, I can tell you patients will be enthusiastic about its availability.

In terms of the risks associated with this drug, the NCA is presently encouraged by the preliminary studies of RU486, which so far show the drug to be safe and effective in treating Cushing's. However, we would support a large controlled clinical trial/trials, managed by qualified endocrinologists who are viewed by their peers as experts in the treatment of this disease. One of those experts, Dr. Mary Lee Vance, associate professor of Medicine at the University of Virginia at Charlottesville, puts it this way:

"Clinical research of RU486 in the United States has been very limited and this needs to be changed. The Endocrinology community would welcome this opportunity to study this drug in detail to determine its efficacy and safety. This is only possible if the drug is made available to the appropriate investigators and I fully support any efforts to permit these needed studies."

In terms of the controlled use of RU486 in Cushing's studies, and possibly eventual expanded treatment, the NCA anticipates that the drug would only be available through a highly trained physician. This is not a drug that can or should be used without strict medical supervision - much like other treatments for Cushing's. We see the availability of RU486 as a long-term benefit to Cushing's patients who need it, and we also see this drug as posing no public health problems in the United States.

In support of these views, we are including a sampling of letters from some of the 44 physician experts who are on the NCA's physician referral list. These endocrinologists, as you can see, are enthusiastic about the future clinical trials and possible availability of this drug for their patients in the future. The NCA is enthusiastic too because we hope that RU486 will soon be another medical option in the list of treatments used to combat this devastating endocrine disorder. Thank you for asking us here today, and we thank you for your time and attention.

SECTION OF ENDOCRINOLOGY
Richard Horton, M.D.
Professor of Medicine
Chief, Section of Endocrinology
Telephone (213) 226-4635

November 6, 1990

Andrea Hecht
National Cushing's Association
46201/2 Van Nuys Blvd.
Sherman Oaks, CA 91403

Dear Ms. Hecht,

RU 486 is an orphan drug that has an action by blocking the glucocorticoid receptor. It thus effectively prevents the hormone cortisol from acting. In Cushings Syndrome, it could potentially block the action of cortisol and thus reverse and control the disease. The standard method of treatment is surgery either on the pituitary or adrenal gland depending on the site of the tumor.

It is difficult to currently place RU 486 in perspective, since surgical therapy usually is effective when the diagnosis is precise. There are however, some patients where surgery is not possible or acceptable. Also, there is a form of Cushings due to cancer of the lung or other organs, where RU 486 could be of considerable use.

I certainly favor the availability of this drug from a French manufacturer, for use as an investigational tool in order to find its proper use in Cushings syndrome and perhaps in other psychiatric disorders where cortisol production is excessive.

Sincerely,

Richard Horton, M.D.
Chief, Division of
Endocrinology and
Metabolism

RH/mck

THE UNIVERSITY OF UTAH

William D. Odell, M.D., Ph.D.
Chairman, Department of Internal Medicine
Professor of Medicine and Physiology

November 1, 1990

Andrea Hecht
National Cushing's Association
4620 1/2 Van Nuys Blvd.
Sherman Oaks CA 91403

Dear Ms. Hecht:

I am writing in reply to your letter of October 29, 1990, concerning potential use of RU486 to treat Cushing's syndrome. RU486 is predominantly known as an antiprogesterone medication and was developed for that purpose. Since progesterone is required for early fetal uterine implantation maintenance, short periods of antiprogesterone treatment results in early fetal loss. However, RU486 also binds to the glucocorticoid receptor, and in animal studies can interfere with hydrocortisone (cortisol) action. Since cortisol is the hormone which is overproduced in Cushing's syndrome, RU486 is a potential medical treatment for Cushing's syndrome. Cushing's syndrome has several causes which can be divided into (a) pituitary dependent causes; and (b) non-pituitary dependent causes. The pituitary dependent causes include the common Cushing's disease - a category which is in approximately 80% of patients, caused by a small pituitary adenoma secreting ACTH. In the remaining 20% of patients, diffuse ACTH secreting cell hyperplasia is present. Additional pituitary dependent causes include larger-aggressive ACTH tumors and a rare entity macronodular adrenal disease. The appropriate and optimal treatment for Cushing's disease is selective surgical resection of the causative adenoma when it's present. In patients with pituitary dependent Cushing's who are not curable by such surgery, or who do not have a pituitary tumor, consideration of treatment by various drugs is merited and presently several drugs are in use which inhibit steroid hormone including cortisol synthesis. In such patients an antiglucocorticoid such as RU486 has potential use. Patients with non-pituitary dependent Cushing's syndrome have disorders including ectopic ACTH or CRH production by various cancers, adrenal neoplasms, or micronodular dysplasia (a rare, usually congenital disorder). Whereas the adrenal tumors are usually resectable, many patients with ectopic ACTH syndrome have unresectable tumors and are candidates for drug therapy, including potentially RU486.

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However, RU486 in doses which have antiglucocorticoid activity, also exhibits antiprogesterone effects. It is possible or even likely that further basic chemical research will result in development of more selective antiglucocorticoid drugs. Such drugs would be more attractive for potential medical therapy of Cushing's syndrome than would RU486. Finally, RU486 is known to bind to glucocorticoid and progesterone receptors and to form a drug-receptor complex, which in turn appears to bind to nuclear DNA, just as the native glucocorticoid-receptor complex does. The long-term effects of such treatment are, of course, unknown at present.

In summary, RU486, a potent anti-progesterone drug, is also an antiglucocorticoid drug and potentially has value in treatment of some patients with Cushing's syndrome.

Sincerely yours,

William D. Odell

William D. Odell, M.D., Ph.D.
Professor of Medicine and Physiology
Chairman, Department of Internal Medicine

WDO/mg

UNIVERSITY OF VIRGINIA
HEALTH SCIENCES CENTER
DEPARTMENT OF MEDICINE

November 5, 1990

Ms. Andrea Hecht
National Cushing's Association
4620 1/2 Van Nuys Blvd.
Sherman Oaks, CA 91403

Dear Ms. Hecht:

Thank you for your letter of October 29, 1990 requesting my opinion of the use of the cortisol receptor antagonist, RU 486, in the treatment of patients with Cushing's Syndrome. I would like to address your questions in the order posed.

I think this compound should be made available to the medical community as soon as possible for use in controlled studies of patients with Cushing's Syndrome for use as a pre-operative agent to restore patients to a functionally normal glucocorticoid state and for use in those patients in whom surgery has failed or in whom surgery cannot be performed (e.g., elderly, debilitated or patients with metastatic disease). As you know, the medical and psychological consequences of chronically elevated cortisol and its effects are extremely detrimental. Thus, a drug which can minimize these effects, without significant side effects, is much needed.

I do not think this, or any other drug, should be administered before it has undergone rigorous controlled studies to demonstrate its efficacy and safety. The preliminary studies of RU 486 for the treatment of Cushing's Syndrome are very promising and suggest that this is a safe and effective drug. However, a large experience, with controlled clinical trials, has not been performed, and this needs to be done. Thus, I do not think this drug should be administered by anyone other than a qualified physician who has experience with the treatment of Cushing's Syndrome. Since this drug blocks the effects of cortisol, it is vital that information be obtained regarding the appropriate dose which does not produce functional adrenal insufficiency and its consequences. This can only be accomplished with well-designed, clinical trials with close monitoring of the recipients of this drug.

Clinical research of RU 486 in the United States has been very limited and this needs to be changed. The Endocrinology community would welcome the opportunity to study this drug in detail to determine its efficacy and safety. This is only possible if the drug is made available to the appropriate investigators and I fully support any efforts to permit these needed studies.

Mary Lee Vance, M.D., Associate Professor of Medicine, Division of Endocrinology and Metabolism
Health Sciences Center, Box 511, Charlottesville, Virginia 22908 804-924-2248(FAX 804-982-3626)

I estimate that in my own practice of academic Endocrinology, that 5 to 10 patients per year may benefit from a trial of RU 486, as pre-operative treatment or for chronic therapy because of metastatic disease or inability to undergo surgery. The currently available drugs are not completely satisfactory in that there are significant side effects or escape from inhibition of cortisol synthesis. Thus, a drug which blocks the effects of cortisol would be an invaluable addition to our medical armamentarium.

I do not understand why this drug has not been made available in the United States as an investigational agent since it appears to be very effective and without toxicity (in the doses reported). Therefore, it seems that its unavailability for proper studies is incongruous. I think that any effort to make this drug available for study is appropriate and should be encouraged at every level.

I hope I have been addressed your questions regarding the potential usefulness of RU 486 in clinical medicine. Please feel free to contact me should you have questions. All best wishes in your endeavors.

Yours sincerely,

Mary Lee Vance

Mary Lee Vance, M.D.
Associate Professor of Medicine

MLV/mlv

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or 936-5958

November 8, 1990

Andrea Hecht
National Cushing's Association
4620 1/2 Van Nuys Blvd
Sherman Oaks, CA 91403

Dear Ms. Hecht:

This is in response to your letter of October 29, 1990, concerning the availability of RU-486 for the treatment of patients with Cushing's syndrome. The availability of RU-486 would be important for both research applications and treatment of patients with types of Cushing's syndrome not responsive to other forms of therapy. I feel that RU-486 should not be used without physician supervision and that its use should be restricted under prescription for specifically defined conditions. As a glucocorticoid receptor antagonist, RU-486 is a useful agent for studying physiological and metabolic aspects of cortisol secretion and the hypothalamic pituitary adrenal axis. From the clinical standpoint, the drug would be useful in treating patients with ectopic ACTH syndrome or adrenal carcinoma who are not candidates for definitive or paliative surgical treatment or who have failed to respond to other types of adrenal inhibitors. The clinical research data available on RU486 indicates that this compound has been effective in ameliorating the metabolic effects of hypercortisolemia in such patients. The unavailability of RU-486 deprives these patients from palliation of their condition.

I am

Sincerely yours,

David E. Schteingart, M.D.
Professor

DES/jeh

Cushing's Syndrome

Fact Sheet

NIDDK

Cushing's syndrome is an endocrine, or hormonal, disorder. Although symptoms vary from person to person, most patients have upper-body obesity, severe fatigue and muscle weakness, high blood pressure, backache, elevated blood sugar, easy bruising, and bluish-red stretch marks on the skin. In women, there may be increased growth of facial and body hair, and menstrual periods may become irregular or stop completely.

Cushing's syndrome is caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol. For this reason, the disorder is sometimes called "hypercortisolism."

Cortisol is normally produced by the adrenal glands, located just above the kidneys. It belongs to a class of hormones called glucocorticoids, which affect almost every organ and tissue in the body. Scientists think that cortisol has possibly hundreds of effects in the body. Among its vital tasks, cortisol:

- helps maintain blood pressure and cardiovascular function;
- helps slow the immune system's inflammatory response;
- helps balance the effects of insulin in breaking down sugar for energy; and
- helps regulate the metabolism of proteins, carbohydrates, and fats.

One of cortisol's most important jobs is to help the body respond to stress. In fact, the adrenal glands naturally produce more cortisol during stress. High levels of the hormone normally occur in women during the last 3 months of pregnancy and in highly trained athletes. Increased cortisol levels also are found in people suffering from depression, alcoholism, malnutrition, and panic disorders.

To understand the different ways that cortisol production can go wrong, it helps to look at how hormones normally do their work. Endocrine glands differ from other organs in the body because they release hormones into the bloodstream. Hormones travel through the blood, instructing cells in other parts of the body to release another hormone or to perform a specific function. Among the major endocrine glands are the thyroid, parathyroid, thymus, pituitary, and adrenals. Together, they play a major role in growth, metabolism, reproduction, and overall health.

The leaders in this carefully balanced performance are the brain's hypothalamus and the pituitary gland, a bean-sized organ at the base of the brain. First, the hypothalamus sends "releasing hormones" to the pituitary gland. The pituitary responds by secreting other hormones that regulate growth, thyroid function, and sex hormones such as estrogen and testosterone. One of the pituitary's main duties is to secrete ACTH (adrenocorticotropin), a hormone that stimulates the adrenal glands. When the adrenals receive the pituitary's signal in the form of ACTH, they respond by producing cortisol. Completing the cycle, cortisol then signals the pituitary to lower secretion of ACTH.

Normally, the amount of cortisol released by the adrenals is precisely balanced to meet the body's daily needs. If something goes wrong during this process—for example, with the adrenals, or their regulating switches in the brain (the pituitary gland or the hypothalamus)—cortisol production can go awry.

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL INSTITUTE OF DIABETES & DIGESTIVE & KIDNEY DISEASES

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Causes

Exposure to too much cortisol can occur for different reasons. A common cause of elevated cortisol is the long-term use of glucocorticoid hormones such as prednisone for the treatment of inflammatory illnesses like rheumatoid arthritis. People who have taken these hormones for a long time may develop the symptoms of Cushing's syndrome, for example, the rounded or "moon face" and muscle weakness.

Elevated levels of cortisol also can be traced to abnormalities of the pituitary gland or the adrenal glands. High cortisol production also can be caused by tumor cells that release ACTH, in turn signaling the adrenals to overproduce cortisol. Each of these causes is discussed in more detail below.

Pituitary Adenomas
Most cases of Cushing's syndrome are caused by benign, or noncancerous tumors of the pituitary gland called adenomas, which secrete increased amounts of ACTH. Most patients have a single adenoma. This form of the syndrome, known as "Cushing's disease," afflicts more women than men. Adenomas are unlikely to spread; rarely, however, some pituitary tumors have the features of cancer, including the ability to spread.

Ectopic ACTH Syndrome
About 17 percent of Cushing's syndrome cases are due to the production of ACTH by various types of potentially malignant tumors that arise in different parts of the body. By far, the most common form of ACTH-producing tumor is oat cell, or small cell, lung cancer, which accounts for about 25 percent of all lung cancer cases. Other, less common types of cancer that can produce ACTH are thymomas, carcinoid tumors, pancreatic islet cell tumors, and medullary carcinomas of the thyroid.

Adrenal Tumors
In about 15 percent of patients with Cushing's syndrome, the cause can be traced to an abnormality of the adrenal glands, most often an adrenal tumor. In about one-half of these cases, the tumors are noncancerous growths of adrenal tissue, called adrenal adenomas, which release excess cortisol into the blood.

Adrenocortical carcinomas, or adrenal cancers, are the least common cause of Cushing's syndrome, accounting for about 7 percent of cases. They tend to occur in children. Cancer cells secrete excess levels of several adrenal cortical hormones, causing cortisol and adrenal androgen levels to remain elevated. Adrenal carcinomas also can be marked by very high hormone levels and rapid development of symptoms.

Incidence

Cushing's syndrome is relatively rare. It affects about 10 people per million population every year, or approximately 1 in 5,000 hospital admissions, with most cases occurring between the ages of 20 and 50 years.

About 70 percent of reported cases are diagnosed with pituitary adenomas that overproduce ACTH (Cushing's disease). This form of the syndrome affects more women than men at a ratio of 5:1.

The ectopic ACTH syndrome, caused by ACTH-producing tumors, is responsible for about 17 percent of the cases of Cushing's syndrome. Of these, over 50 percent are due to lung tumors, with a 3:1 ratio of males to females.

Adrenal tumors account for the remainder of cases, occurring in about two per million population annually. The average age of onset is about 40 years.

Symptoms

There is no single symptom shared by all patients with Cushing's syndrome, although some features of the disorder occur more often than others.

Obesity
The most common symptom is weight gain, with rounding of the face and increased fat in the neck and above the collar bone, while the arms and legs tend to stay thin. Obesity associated with poor growth is most common in children.

Skin
Skin changes also are common in Cushing's syndrome. The cheeks redden as the skin becomes thin, making the blood vessels more visible. The thin, fragile skin breaks easily, and ulcers may arise from minor injury. The ulcers may persist for a long time because of poor wound healing. Easy bruising and bluish-red stretch marks, which often appear on the abdomen, thighs, buttocks, arms, armpits, and breasts, result from weakened connective tissue. Connective tissue not only provides the supportive framework of the body and its internal organs, but it is a major structural component of arteries and veins as well as the skin.

Excess Hair Growth
In women, excess hair growth, or hirsutism, often appears on the face, neck, chest, abdomen, and thighs. It occurs in about 80 percent of women with Cushing's syndrome.

Menstrual Disorders
Menstrual disorders are common. Periods become irregular and often stop. In men, there is decreased fertility with diminished or absent libido.

High Blood Pressure
Blood pressure above the normal range, or hypertension, occurs in 85 percent of Cushing's patients. More than 50 percent of patients have elevated diastolic pressure, and practically all patients have elevated systolic pressure. High blood pressure is associated with increased atherosclerosis, a buildup of fat in the arteries.

Muscle and Bone Weakness
Severe fatigue and weak, fragile muscles are characteristic of Cushing's syndrome. Backache is common due to osteoporosis, a weakening of the bones resulting from decreased bone mass. In Cushing's syndrome, rib fractures are frequent, and vertebral (spinal column) compression fractures may occur during routine activities such as bending, lifting, or rising from a chair.

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High Blood Sugar
High blood sugar, or hyperglycemia, is seen in 80 percent of patients with Cushing's syndrome following the oral glucose tolerance test. However, diabetes mellitus occurs in less than 20 percent of people with Cushing's syndrome, and usually only in those with a family history of the disorder.

Diagnosis

The diagnosis of Cushing's syndrome is based on a review of the patient's medical history, physical examination, laboratory tests, and often x-ray exams of the adrenal or pituitary glands. The aim of these tests is first to determine whether excess levels of cortisol are present and then to establish the cause.

24-Hour Urinary Free Cortisol Level
This is the most specific test for diagnosing Cushing's syndrome. The patient's urine is collected over a 24-hour period and then tested for the amount of cortisol. Levels higher than 100 micrograms a day for an adult suggest Cushing's syndrome. (Persons suffering from depression or alcoholism, who tend to produce higher than normal levels of cortisol, may need further testing to confirm a diagnosis of Cushing's syndrome.)

Once Cushing's syndrome has been diagnosed, it is important to determine its cause. Various other tests are used to find the abnormality that leads to excess cortisol production. The choice of test depends in part on the preference of the endocrinologist or the center where the test is performed. Two very specialized tests that may be used are described below.

Dexamethasone Suppression Test
In this test, dexamethasone, a synthetic cortisol, is given by mouth every 6 hours for a period of 4 days. For the first 2 days, low doses of dexamethasone are given, and for the last 2 days, higher doses are given. The normal response after taking dexamethasone is a drop in blood and urine cortisol levels. Depending on the cause of Cushing's syndrome, different responses of cortisol to dexamethasone are obtained. The dexamethasone suppression test helps to distinguish patients with pituitary adenomas from those with ACTH- or cortisol-producing tumors.

The dexamethasone test can produce false-positive results in response to depression, alcohol abuse, high estrogen levels, acute illness, and stress. Conversely, drugs such as phenytoin and phenobarbital may cause false results in response to dexamethasone suppression. For this reason, patients should stop taking these drugs for at least 1 week before the test is performed.

CRH Stimulation Test
The corticotropin-releasing hormone (CRH) stimulation test is a relatively new diagnostic tool that also may be used to identify the cause of Cushing's syndrome. Patients with pituitary adenomas, after receiving an injection of CRH, usually have a rise in blood levels of ACTH and cortisol. This response is rarely seen in patients with ectopic ACTH syndrome and practically never in patients with cortisol-secreting adrenal tumors.

Direct Visualization of Endocrine Glands
Doctors use different imaging tools to reveal the size and shape of the pituitary and adrenal glands. The most common are the CT (computerized tomography) scan and MRI (magnetic resonance imaging). A CT scan produces a series of x-ray pictures giving a cross-sectional image of a body part. MRI also produces images of the internal organs of the body but without exposing the patient to ionizing radiation. A CT scan or MRI of the pituitary gland may help determine if a tumor is present, causing an overproduction of ACTH. Occasionally, doctors use a special radioisotope procedure, known as the iodocholesterol scan, to view the adrenal glands. If these tests do not establish the source of ACTH, some centers are experienced in performing catheterization procedures that sample the blood leaving the pituitary gland to determine if the pituitary is the source of high ACTH.

Treatment

Treatment of Cushing's syndrome depends on the specific reason for cortisol overproduction. If the cause is long-term use of glucocorticoid hormones to treat another disorder, the doctor will gradually reduce the dosage until the symptoms are under control. Once control is established, the daily dose will be doubled and given on alternate days.

Pituitary Adenomas
Several therapies are available to treat the ACTH-secreting pituitary adenomas of Cushing's disease. The most widely used treatment is removal of the tumor by surgery, known as transsphenoidal adenomectomy. Using a special microscope and very fine instruments, the surgeon approaches the pituitary gland through a nostril or an opening made in the bridge of the nose. Because this is an extremely delicate procedure, patients are often referred to centers specializing in this type of surgery. The success, or cure, rate of this procedure is over 80 percent. When surgery fails, it is usually because the CT scan or MRI is unable to identify the small adenoma. After pituitary surgery, there is a natural but temporary drop in the production of ACTH, so patients must be given a synthetic glucocorticoid hormone called hydrocortisone. Most patients can stop this replacement therapy in less than 1 year.

For patients in whom transsphenoidal surgery has failed or who are not suitable candidates for surgery, radiotherapy is another possible treatment. Radiation to the pituitary gland is given over a period of 6 weeks, with improvement occurring in 40 to 50 percent of adults and up to 80 percent of children. It may take several months before patients feel better from radiation treatment alone. However, the combination of radiation and the drug mitotane (Lysodren®) can help speed recovery. Mitotane suppresses cortisol production and lowers plasma and urine hormone levels. Treatment with mitotane alone can be successful in 30 to 40 percent of patients. Other drugs used alone or in combination to control the production of excess cortisol are aminoglutethimide, metyrapone, and ketoconazole. Like all drugs, each has its own set of side effects that doctors consider when prescribing therapy for individual patients.

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Ectopic ACTH Syndrome

To cure the overproduction of cortisol caused by ectopic ACTH syndrome, it is necessary to eliminate all of the cancerous tissue that is secreting ACTH. The choice of cancer treatment—surgery, radiotherapy, chemotherapy, immunotherapy, or a combination of these treatments—depends on the type of cancer and how far it has spread. Since ACTH-secreting tumors (for example, small cell lung cancer) may be very small or widespread at the time of diagnosis, cortisol-inhibiting drugs like mitotane form an important part of treatment. In some cases, if pituitary surgery is not successful, surgical removal of the adrenal glands (bilateral adrenalectomy) may take the place of drug therapy.

Recently, researchers have found that a glucocorticoid antagonist, RU 486, is effective in fighting the excessive effects of cortisol that cause Cushing's syndrome. RU 486 is still an investigational drug, however, and its use is limited to clinical trials.

Adrenal Tumors

Surgery is the mainstay of treatment for benign as well as cancerous tumors of the adrenal glands.

Research in Cushing's Syndrome

The National Institutes of Health (NIH) is the biomedical research arm of the Federal Government. It is one of seven health agencies of the Public Health Service, which is part of the U.S. Department of Health and Human Services. Several components of NIH—the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke, and the National Cancer Institute—conduct and support research on Cushing's syndrome and other disorders of the endocrine system.

NIH-supported scientists are conducting intensive research into the normal and abnormal function of the major endocrine glands and the many hormones of the endocrine system. One important NIDDK-supported study by Dr. Wylie W. Vale and colleagues at the Salk Institute for Biological Studies in La Jolla, California, led to the identification of corticotropin-releasing hormone (CRH), which instructs the pituitary gland to release ACTH. This finding enabled Dr. George P. Chrousos and coworkers at the NICHD to develop the CRH stimulation test, which is increasingly being used to identify the cause of Cushing's syndrome. Using the dexamethasone suppression test, doctors are able to diagnose the cause of Cushing's syndrome in 80 percent of patients. With the CRH stimulation test alone, they can accurately diagnose the cause in 85 percent of cases. By using the dexamethasone suppression test and CRH stimulation test together, they are able to diagnose Cushing's syndrome with 98 percent accuracy, according to a recent NIH study.

NIH scientists are continuing their efforts to improve the diagnosis and treatment of Cushing's syndrome. Current research is targeted not only at identifying new hormones, but also understanding their precise functions. Researchers also are focusing on the role of

receptors, which are large complex molecules either on the surface of or within target cells to which hormones must attach to be effective.

One goal of future research is to find ways to cure Cushing's syndrome without surgery. For example, it may be possible to destroy pituitary tumors selectively by binding a hormone like CRH, which precisely targets pituitary tissue, with a tumor-killing toxin or monoclonal antibody.

Current NIH Studies

Scientists are treating patients with Cushing's syndrome at the NIH Warren Grant Magnuson Clinical Center in Bethesda, Maryland. Physicians who are interested in referring a patient with Cushing's syndrome may contact Dr. George P. Chrousos, Developmental Endocrinology Branch, NICHD, Building 10, Room 10N262, Bethesda, Maryland 20892, telephone (301) 496-4686.

Suggested Reading

The following materials can be found in medical libraries, many college and university libraries, and through interlibrary loan in most public libraries.

Forsham, Peter H. and Tyrrell, J. Blake, "Cushing's Syndrome," in *Current Diagnosis*, edited by Rex B. Conn. Philadelphia, W.B. Saunders Company, 1985, pp 863-867.

Chrousos, George P., "Cushing's Syndrome," in *Conn's Current Therapy*, edited by Robert E. Rakel. Philadelphia, W.B. Saunders Company, Philadelphia, 1987, pp 495-498.

Kohler, Peter O., ed. *Clinical Endocrinology*, New York, John Wiley & Sons, 1986.

Braunwald, Eugene et al., eds. *Harrison's Principles of Internal Medicine*, 11th edition, New York, McGraw-Hill Book Company, 1987, pp 1760-1764.

NCI Research Report: Cancer of the Lung. Prepared by the Office of Cancer Communications, National Cancer Institute, NIH Publication No. 86-526.

Other Resources

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4620½ Van Nuys Boulevard
Sherman Oaks, California 91403
(818) 788-9235 or (818) 788-9239
Andrea Hecht, President

[redacted]

8

[redacted]

This fact sheet was written by Eileen K. Corrigan of NIDDK's Office of Health Research Reports. The draft was reviewed by Dr. George P. Chrousos, National Institute of Child Health and Human Development, and by Dr. Richard Horton, University of Southern California Medical Center.

This fact sheet is not copyrighted. Readers are encouraged to duplicate and distribute as many copies as needed. Single copies may be obtained from the Office of Health Research Reports, NIDDK, Building 31, Room 9A04, Bethesda, Maryland 20892, (301) 496-3583.

NIH Pub. No. 89-3007
April 1989

BEVERLY ZAKARIAN

STATEMENT TO CONGRESSMAN WYDEN'S SUBCOMMITTEE RE: RU-486

Thank you for asking me to appear before you, and offering me the opportunity to explain my experience and how it applies to the present situation of RU-486.

In 1985, I was one of 18,500 women diagnosed with ovarian cancer. Thanks to advances in the treatment of ovarian cancer, I am one of the 7,200 who is still alive, five years later.

I have survived, but I have changed: I've committed myself to securing for others the opportunity I had to save my life.

When my cancer was discovered, I was a designer and illustrator, and the mother of a 15-year old daughter. As most ovarian cancers are, it was discovered accidentally, in the course of a prophylactic hysterectomy. It was in Stage 3, which means that there were multiple tumors above the pelvis, into the abdomen. The prognosis on the operative report was "Guarded".

Two weeks after the surgery, I was readmitted to the hospital for chemotherapy. What did I know about chemotherapy??? Nothing--except that it was supposed to save my life. So I unquestioningly followed the doctor's orders. I had one ravaging cycle of high-dose chemotherapy with cis-platinum, then was sent home to recover-- and to prepare for the second cycle.

Before 1979, there was NO effective treatment for ovarian cancer. A fortuitous discovery by a researcher led to the development of cis-platinum. Prior to that, a good response to

More....

the treatment drugs then available was 3-6 months extension of life!

Cis-platinum, however, has several serious drawbacks: the heavy metal molecule is toxic to the kidneys, so the patient must be hydrated for a day or two prior to the chemotherapy. The patient is stuffed full of fluid intravenously, the treatment is given, then every effort is made to dehydrate the patient in order to remove the toxic material quickly. During the course of these ministrations, the patient is also nauseated, vomiting, and usually has diarrhea. With any leftover time, she can contemplate her forthcoming baldness!

I was able to recover from these side effects, because what followed made them seem minimal: I began to experience hearing problems-- loud noises were painful; the sound of jangling keys would drive me mad; eventually even normal conversational levels became intolerable. Deafness, I learned, is a possible side-effect of cis-platinum.

At the same time, I was terrified to realize that my right index finger suddenly became paralyzed. As an artist, this is my most important finger for fine motor control. No matter how I willed the movement to happen, I couldn't bend the joints.

Nerve damage or neuropathy, I found, is another expected side-effect of cis-platinum. Women who are treated for long periods of time with this agent can experience permanent numbness in their feet and hands. The comedienne Gilda Radner, who died of ovarian cancer, was one of these women, and she wrote, poignantly, in her book about her cancer, that she had trouble

writing because her hands were so numb. I began to fear that the treatment was going to kill me before the cancer could!

Quite by chance, I read a brief report in the newspaper that announced the start of widespread clinical trials in the US of a drug called carbo-platinum, that was already the standard treatment in other medically advanced countries. It was an analog of cis-platinum, but reportedly far less toxic to nerves and kidneys, and ~~thus~~ did not require the elaborate hydration of the patient, and thus could be done on an out-patient basis. Although developed by Americans, it was new to America, and had been in clinical trials for four years, since 1981.

That was when I realized that I had choices to make, and that the choices could affect the outcome of my treatment. I sought a new oncologist; at the same time, I attempted to get myself onto one of the clinical trials. Probably this would not have been successful, because I had already had the one treatment with cis-platinum, and the protocols demanded otherwise.

My new doctor, however, was able to secure the investigational drug for me on a "compassionate release" basis, because it was clear that the first treatment was too toxic for me to tolerate. And there was no other possible treatment available.

Consider the situation for a moment: a very sick person, whose life is at risk, has only ONE treatment available. That treatment can destroy the patient's quality of life, should she survive. How can anyone have to make that choice?

More.....

It's imperative that there be as many therapeutic drugs available to cancer patients as there are drugs effective against cancer.

People can become resistant to drugs after extended treatment. Combination chemotherapy REQUIRES that a patient be treated with different drugs, because they attack the cancer by different means and at different times in the tumor's growth. Some cancer drugs are themselves carcinogens, and cannot be administered too long, for fear of incurring secondary cancers. Every case of cancer is an individual one, and people need individualized treatment with whichever drug works for them.

Thanks to my access to the new anti-cancer agent, I am able to stand here before you and speak for millions of your--and my--constituents. The Cancer Patients Action Alliance supports research with RU-486. It may save someone's life some day. We don't know yet-- and we won't know unless research with this agent continues. Any drug that shows promise must be investigated. Research must absolutely not be hindered by political or religious factions. There are 1 million new cases of cancer a year, and cancer does not ~~strike~~ fall along political or religious lines. Catholics, Protestants, Jews, Muslims, all the ethnic groups that comprise our diverse population, all want to survive cancer when it strikes.

END

HELEN BYRNE REPORT TO SUBCOMMITTEE ON RU486

I am the Vice-President of the Cancer Patients Action Alliance known as CANACT. I would like to relate to you my experience with breast cancer. In January, 1982, I had a spontaneous eruption of what I hoped was a very large cyst or carbuncle on top of my left breast. I was terrified that it was neither of these but was cancer. Instead of doing what most people would do - run to the doctor - I went ahead with my planned and paid for trip to Rome. If it was a cyst, it would wait. If it was cancer, I was going to die anyway.

In early April, I finally went to my family physician, who, after one look made an appointment for me with a surgeon. The surgeon agreed, it was cancer. I needed a mastectomy. Possibly, it would have to be bilateral. Maybe, after surgery, I would need a short regimen of chemotherapy. He made arrangements for a pre-hospitalization work-up in mid May.

When a friend and co-worker, who had had ovarian cancer, learned of my problem, she insisted I go to see her oncologist, Dr. Ezra Greenspan. On her insistence and because I was too traumatized to argue, I went to Dr. Greenspan on Friday afternoon April 23rd. After his examination he sent me that same day to Dr. James Gaston, a surgeon, whose specialization is breast cancer. Dr. Gaston examined me and made arrangements for my hospitalization that Sunday. Surgery was scheduled for Tuesday, April 27. On Tuesday, I had a bilateral mastectomy with the

removal of 38 lymph nodes. In other words, I had Stage III breast cancer.

I remained in the hospital and had my first chemotherapy on Sunday May 2. I remember that day quite well since it was my birthday. The following week, I went home and began an intensive regimen of chemotherapy which consisted of methotrexate, fluorouracil and cytoxen. This was all prior to the date the other surgeon had arranged for my pre-hospitalization work-up. I know now that he probably thought it was a waste of time. With my advanced condition, I probably wasn't going to make it anyway.

A few weeks after I started the chemotherapy, all my hair fell out. I was completely devastated. It was just one more blow. I didn't feel human. I wanted to die. Now, not only would I have to wear a prosthesis, I would also have to wear a wig. Today, I still get incensed when I see fund raisers exploit children, who have lost their hair because of chemotherapy, just to raise money. They can't know the insult added to injury that has been inflicted.

While I was at home feeling sorry for myself, I received a phone call from one of my agency's heads. He wanted to tell me, before I heard it on the grapevine, that there was going to be a major survey of the Bureau I headed to determine if the Bureau should be decentralized. However, I was not to worry, it would not affect me or my job as Director. I thought, he either thinks they removed my brain or since I have cancer I will die and he better do something about my office. So five weeks after my

surgery, still bandaged and still with many stitches in, I returned to work. While working, I continued with chemotherapy, both orally and intravenously.

Some 6 months after my surgery, I thought I ought to stop in to see my family physician to let him know how I am coming along. When I walked into his office unannounced, he had his back to me. When he turned around and saw me, he started to cry. He thought I had died and no one had told him.

My chemotherapy lasted for a year and a half. Quite different from the original surgeon's opinion of a short regimen of chemotherapy. My hair grew back. My Bureau stayed in tact and I have advanced to head an even larger Bureau. Since then I take tamoxifen, a chemopreventive, twice a day and I will continue to take it for the rest of my life.

Here I am 8 years later, alive and still working. But what has happened in 8 years about breast cancer. From 1982, when I was diagnosed, to 1986 the breast cancer incidence rates have increased 15%. With improved detection - mammography -, since 1986, there has been a large increase in the detection of early cancer. But what about survival. With improved early detection, has the death rate dropped significantly? No! In 1983, the death rate was 7%. In 1986, the death rate was 6.4% - A drop of only .6%. There are 150,000 new breast cancer cases each year in the U.S. In the past 2 years, 83,000 women have died, 44,000 last year. Of these 11,000 were young women, many with children.

I have come today because of a debate over a drug called

RU486, which is a possible preventive of breast cancer. But the drug requires research and testing before it can be administered. However, there is a question of whether or not this drug should even be tested because of one effect of RU486 - it may cause abortions.

Once this effect was discovered, the Pro-Choice lobby wanted testing to begin in the U.S. Some testing has been done in Europe. The Pro-Choice lobby sees RU486 as an answer to their dilemma. But the Pro-Life lobby wants testing banned because it will take the lives of the unborn. Both groups are involved in lobbying because they see the issue as abortion. Both groups have put aside as secondary, the women's issue - Breast Cancer.

~~practicing~~ Catholic who is unalterably opposed to ~~abortion. The issue here is not abortion.~~ The issue is the life or death of ~~women with~~ breast cancer. Without testing, we will ~~never know if RU486 is the solution~~ to breast cancer. We must ~~not continue to allow women to die unnecessarily~~ because of a ~~variety of agendas~~. There is a major moral agenda here. Should ~~we turn our backs~~ on women and let them continue to suffer and die because we stop ~~research~~.

The argument about an evil effect does not work. Many prescribed and over the counter drugs are taken for purposes other than those intended such as: sleeping pills, diet pills, cough medicine, rubbing alcohol and even hair spray. RU486, if tested and approved, would be prescribed by physicians for breast cancer.

BEST AVAILABLE COPY

I am not a theologian but I do know that in theology there is a theory of double effect. That states we must look to the greater good even if some evil happens. If RU486, is tested and approved and saves the lives of women, many of whom have had and are raising children, then that is the greater good.

The purpose of CANACT is to bring to the attention of the public, media and legislators the need to move forward on drug testing for cancer prevention or cure. Why is it possible for Europe and Canada to have drugs for cancer prevention and cure tested, approved and on the market years before these same drugs are tested, approved and available to the American public. This delay is causing the deaths of thousands of Americans who can't afford to go to Europe or Canada for treatment.

The physician and oncologist is the expert. When drugs are tested and approved, the decision on combination use should be left to them and the patient. Cancer patients should not have to be patient. We should not have to die quietly while the bureaucracy drags its feet and groups with other agendas divert the real focus. The prevention and cure of cancer.

Thank you for inviting me here today to address the committee on behalf of CANACT and as a breast cancer survivor. My experience is not unique. I was lucky the chemotherapy I was given saved my life. Not everyone who takes chemotherapy has the same reaction to similar drugs. Others may not have been able to tolerate the combination of drugs that were given to me. What works for one does not work for all. We all recognize the need

for careful testing of drugs before they are approved. But we are at war. We have 150,000 casualties every year and 44,000 fatalities. These numbers are on the rise. There is no excuse for not testing and exploring every avenue until such time as women no longer have to live in fear of breast cancer.

Testimony before the

U.S. House of Representatives

Committee on Small Business
Subcommittee on Regulation,
Business Opportunities and Energy

November 19, 1990

Regarding

The Food and Drug Administration's
Automatic Detention Import Alert on RU-486

Statement of

Myron Allukian, Jr., DDS, MPH
Immediate Past President

on behalf of

The American Public Health Association
1015 15th Street, NW
Washington, D.C. 20005
(202) 789-5648

Congressman Wyden and Distinguished Members of the Subcommittee on Regulation, Business Opportunities and Energy.

My name is Myron Allukian, Jr., and I am here today on behalf of the American Public Health Association. I am the Immediate Past President of the American Public Health Association and I was also a member of the scientific delegation that visited the manufacturer of RU-486 earlier this year.

The American Public Health Association is the oldest and largest public health association in the world with a collective membership of over 52,000 health professionals representing some 77 different health disciplines. APHA is also the Secretariat for the World Federation of Public Health Associations.

The primary purpose of the American Public Health Association (APHA) is to promote and protect the health of the American people. APHA is deeply concerned about the health status of all Americans, and the cost, quality and access to health services for all segments of our population.

Our nation spends more than $660 billion a year for health services -- more than any other nation in the

world. In spite of these expenditures, the health status of Americans has not kept pace with other countries. For example, our standing in infant mortality has dropped from 5th to 22nd. There are many reasons that our country is not making the best use of the health dollar, some are endemic to the system and some are bureaucratic or political barriers.

I was surprised to recently learn that the Food and Drug Administration (FDA) issued an automatic detention import alert on RU-486 on June 9, 1989. This is a good example of a bureaucratic barrier that is not in the best interest of the American people. It has a negative effect on cost, quality and access to health care. One of the reasons our country spends much more money on health care than other country in the world is that our health care delivery system is oriented more to tertiary high technology crisis care rather than primary oriented care and preventive services. Our country should use every opportunity to research, develop and implement new and better ways to prevent and treat disease. RU-486 has enormous potential to improve the quality of life for all Americans, especially women and their families. RU-486 should be given every opportunity to be tested, developed, and utilized in our country.

The FDA's position on RU-486 demonstrates a profound

ignorance to the potential of RU-486 and the benefits that it may have for the American people. RU-486 should be treated like any other drug that has demonstrated potential to improve the quality of life. The FDA's import alert sends the wrong message to researchers, academia, health professionals and the public. This will only hurt investigating the potential of RU-486.

This summer I was part of a delegation of American scientists and feminist leaders who met with the President of Roussel-Uclaf, the manufacturer of RU-486. We also met with the health policy leadership of Hoechst, the parent company whose headquarters are in Germany.

I was impressed with their high ideals and concerns about public health and safety. It is important to them that wherever RU-486 is used, that it will be administered properly and not abused. Our visit gave us a better understanding of how RU-486 is currently administered and distributed in France and how it may be utilized in our country. In turn, we were able to answer some of the concerns they had about our health care delivery system and its ability to utilize new technologies.

Over 50,000 women in France have successfully used RU-486, yet it is not available in the United States. RU-486 is a safe, economical, medical alternative to a

surgical procedure. It is easy to administer, does not need anesthesia and allows women more privacy and control over their personal health services.

Other potential benefits of RU-486 have been demonstrated in the treatment of endometriosis, breast cancer, Cushings disease, meningiomas and viral infections. All of these are serious diseases affecting a significant portion of the population. For example,

- o One in ten women will have breast cancer resulting in about 50,000 deaths a year.

The APHA supports the use and testing of new contraceptives and abortifacients such as RU-486. See attachment A, APHA's policy statement. RU-486 does not present any greater opportunity for misuse than any other prescription drug controlled by physicians and researchers. RU-486 to the best of my knowledge has not been misused as an abortifacient. As a matter of fact, its distribution and utilization has been very well controlled and studied resulting in a collection of very high quality data and information.

In my opinion, the primary reason for the overly cautious approach by the French in the distribution of RU-486 is the desire by the manufacturer to have the

strongest possible data base on the effectiveness and safety of RU--486 so that they will not be liable for unfounded legal suits or publicity. RU-486 should not be treated any differently than any other drug. If the political climate is such that the only way that RU-486 could be introduced in the United States is to have similar controls, this would be acceptable with the expectation that reality and a strong data base would make this unnecessary at a future time. In my opinion, it would be possible for our country to have similar controls as those in France if that were necessary.

Politics and the outcry of a minority should not interfere with medical research that has the potential to improve the quality of life for millions of Americans. We must never be afraid to find new and better ways to prevent and treat disease and human suffering. The fact that RU - 486 is also an effective abortifacient is not a rational reason to deny research for other potential benefits to society.

Based on our meeting with Roussel-Uclaf, I would expect the manufacturers of RU-486 to be willing to supply this drug to American researchers. I also believe that they would be willing to supply RU-486 for scientific and other medical uses in the United States without obtaining full approval for the drug as an abortifacient. However,

as most of the studies on RU-486 have been for its use as an abortifacient, it is difficult to understand on what scientific grounds full approval would not be forthcoming.

Unwanted pregnancies in our society continue to be a serious problem. Regardless of one's moral perspective, the facts are disturbing:

o Over 56 percent of the six million pregnancies a year in the US are unintended.

o More than 1.6 million abortions a year occur in the US.

o More than one million teen age girls in the US become pregnant each year, of which over 400,000 have abortions.

o 92% of the pregnancies of single teenagers are unintended.

o 67 percent of teen mothers and their children live in poverty and only one in 50 will finish college.

o Nearly 70 percent of teens do not use contraceptives regularly.

o US girls under age 15 are five time more likely to give birth than their peers in any other developed country.

o 20 percent of teens get pregnant within the first month of their first sexual encounter and 50 percent within six months.

Regardless of one's moral and religious beliefs, the facts vividly portray the lack of our society's commitment to our nation's youth, indigent and high risk populations.

We must be responsive to the needs of our country. It may also interest you to know that the Feminist Majority has collected almost 200,000 signatures in support of RU-486 being made available in the United States. Over 1,000 scientists and health care professionals have also signed these petitions and I submit them for the record.

Our government agencies must be credible and responsible, by making their decisions based on scientific facts not emotions. It is disturbing that the FDA is allowing medical research to be politicized. RU-486 must be treated like any other drug regarding efficacy, public health and safety. We must not deny our nation better ways to prevent and treat serious diseases which effect a significant proportion of the American people. I urge you

to do everything in your power to make RU-486 available in the United States. Thank you.

Attachment A

AMERICAN PUBLIC HEALTH ASSOCIATION
1015 Fifteenth Street, N.W., Washington, D.C. 20005 • (202) 789-5600

Development and Marketing of New Means of Fertility Control

The American Public Health Association,

Recognizing that over half of the world's people have inadequate access to birth control services;[1] and

Recognizing that while current technologies to control fertility are useful, no method is perfect with respect to safety, convenience, side effects, cost, effectiveness, and acceptability;[2-4] and

Recognizing that availability of a wide variety of fertility regulation methods improves family planning program effectiveness and the likelihood that individual users will find a method which meets their needs;[2-4] and

Recognizing that efforts to carry out research development, and marketing of new and improved means of fertility control are hampered by a variety of obstacles such as product liability risks, inordinately slow drug approval processes, funding shortages, and attacks from birth control and abortion opponents;[2-4] and

Recognizing that these obstacles have slowed or halted private and governmental efforts to develop and make available certain technologies (i.e. abortifacients such as RU 486) which may be safer and remain both legal and highly acceptable to large numbers of potential consumers;[5-6] therefore

1. Urges the development of an expanded variety of means of fertility control as a contribution to the improvement of public health;

2. Urges increased public and private funding of a strong research and development effort on the part of publicly supported research organizations and the pharmaceutical industry with the goal of making available all safe and effective fertility control methods;

3. Urges Congress and the Executive Branch to eliminate legal barriers and surmount political pressures which narrow the scope of federally supported fertility regulation research;

4. Urges that drug regulatory decision relating to new means of fertility control be carried out on a timely basis and be based on scientific evaluations of risks, benefits and effectiveness; and

5. Urges the achievement of constructive solutions to the problem of declining access to services because of the effects that product liability claims have had on the availability of supplies and services, recognizing the right of injured individuals to obtain fair compensation and the responsibilities of private industry to develop safe and effective products without discouraging private industry from developing and marketing new means of fertility control.

Adopted in 1988

Statement of the American Medical Association

to the

Subcommittee on Regulation, Business Opportunities, and Energy

Committee on Small Business

U.S. House of Representatives

Presented by:
P. John Seward, M.D.

RE: RU 486

November 19, 1990

American Medical Association
515 N. State Street
Chicago, Illinois 60610

Department of Federal Legislation
Division of Legislative Activities
(312) 464-4775

STATEMENT

of the

AMERICAN MEDICAL ASSOCIATION

to the

Subcommittee on Regulation, Business Opportunities, and Energy

Committee on Small Business

U.S. House of Representatives

Presented by:
P. John Seward, M.D.

RE: RU 486

November 19, 1990

Mr. Chairman and Members of the Subcommittee:

My name is P. John Seward, M.D., and I am a physician in family practice in Rockford, Illinois. I also am a member of the Board of Trustees of the American Medical Association. Accompanying me is Dave Heidorn of the Association's Division of Legislative Activities. The AMA appreciates this opportunity to appear today to discuss the issue of RU 486 availability in the United States.

In the Subcommittee's letter of invitation to appear, you asked that the AMA respond to a number of special questions regarding the drug. In addressing those inquiries, I want there to be a clear understanding of the AMA's policy regarding RU 486 and what we believe to be the current legal status of that drug within the United States.

At its June 1990 meeting, the AMA's House of Delegates adopted the following resolution:

> RESOLVED, That the American Medical Association support the legal availability of RU 486 for appropriate research and, if indicated, clinical practice.

The reason that the Association took this position was our very real concern that politics or ideology could interfere with a well established, legal decision-making process that is and must always be based on good science and proper medical practice, nothing more.

As you well know, RU 486, or mifepristone, which is a steroidal agent being used as an early abortifacient in some countries, has raised deep feelings among both the proponents and opponents of abortion and the prospective use of RU 486 in the United States. It is the AMA's position that any governmental decision regarding this drug, as with all other drugs, must not be influenced by political debates or social issues such as this one. This must not be taken to mean that the AMA supports the widespread availability of RU 486. We do not believe that there has been adequate research to establish that this drug is a safe and effective therapeutic modality. In fact, the central difficulty in evaluating this drug is that no research is being conducted in the United States to determine whether RU 486 has a role in medical practice, and the reason no research is going forward is its manufacturer's decision not to pursue clinical testing of the drug here.

As we understand the current situation, no Investigational New Drug (IND) applications (the legal precondition for a drug to be transported in interstate commerce for the purpose of clinical research) either are pending or have been approved by the Food and Drug Administration (FDA) for RU 486. Since the Federal Food, Drug and Cosmetic Act requires that a drug be proven safe and effective for its intended purpose through well controlled clinical investigations, there is no basis for approval of a New Drug Application to allow the drug to be marketed. Therefore, no

legal basis exists for this drug to be used in the United States for research or in marketing.

The only other basis for allowing importation of RU 486 would be for individual compassionate use. However, it is the AMA's understanding that RU 486 poses a severe risk to patients unless the drug is administered as part of a complete treatment plan under the supervision of a physician. During an appropriate course of treatment with the drug, it is common that three or four visits to a physician are necessary to avoid hemorrhaging and to ensure that a complete abortion has taken place. It also must be taken with a prostaglandin to increase the probability that a complete abortion occurs. Clearly, the importation of RU 486 for personal compassionate use would not be medically desirable given alternative available care methodologies.

These difficulties do not mean that research on RU 486 should not be conducted. On the contrary, we believe that if this drug can be shown to be a safe and effective medical treatment, it should be available for the appropriate care and treatment of patients. There has been some published conjecture that RU 486 may be an effective treatment for other indications besides its use as a contraceptive or abortifacient, including treatment of breast cancer, gynecological malignancies, glaucoma, infertility, and labor induction. While we do not believe this conjecture to be based on any substantiated tests of the drug, RU 486's application to these conditions is certainly possible, although adequate drugs for these conditions already exist. It may even be possible that this drug is useful in treatments about which we have no current knowledge. No one, at this time, can say.

The only way to make these determinations and to establish the safety and efficacy of RU 486, as all other drugs, is to conduct the necessary research and clinical trials required by the FDA to market drugs in the United States. This is a highly effective process established to protect the health, safety, and welfare of the American people. For the same reasons drugs proven to be safe and effective should not be kept out of the United States for political reasons, so also should the high standards we have for drugs not be contravened for political purposes.

Rumors exist that the FDA, due to political pressure, is standing in the way of research on RU 486. We do not believe this to be true. On the contrary, it is the FDA's responsibility to ban a drug that has not met legal and regulatory requirements for importation into the United States. Because RU 486 has not met these requirements, the FDA complied with its charge and acted well within its authority in issuing its June 9, 1989, automatic detention import alert concerning the drug.

As we understand the situation, the actual impediment to research on RU 486 is the manufacturer's unwillingness to make the drug available in the United States. Without the drug, it is impossible to apply for an IND. The manufacturer is reportedly unwilling to allow clinical testing in the United States because of its concerns over the political controversy that has followed this drug and is sure to intensify if research begins in this country. While the French government compelled the French manufacturer to make the drug available in that country, we do not believe that this is a problem that can be easily addressed under our current law.

Conclusion

The AMA stands by the FDA's appropriate application of its legal responsibilities in protecting the health and well being of the American people from unsafe drugs. From our understanding of the current situation, the FDA has acted responsibly in issuing import restrictions for RU 486. At the same time, we would expect that, if an acceptable IND is submitted, the IND would be approved and importation allowed. We hope that the drug can be made available and research eventually can be conducted in this country to determine if the drug is safe and effective for its known uses and whether its use may be appropriate for other medical treatments. It is our primary concern that patients have every opportunity to receive the best possible medical treatment. When possible research into drug therapies does not occur, for whatever reason, the likelihood that the best possible care will not someday be available is greatly increased.

Frankly, we have no answer for this Subcommittee on how to ensure that all appropriate research occurs. Under our current system, which is the world's standard for the development of drugs, the manufacturer is well within its rights to hold the drug from distribution. We can only hope that the political climate will somehow not influence any future consideration of the introduction of RU 486 into the United States.

4239s

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Statement

of

Ronald Chesemore

Associate Commissioner for Regulatory Affairs

Food and Drug Administration

Public Health Service

Department of Health and Human Services

BEFORE THE

Subcommittee on Regulation, Business Opportunities and Energy

Committee on Small Business

U.S. House of Representatives

November 19, 1990

1

Mr. Chairman:

I am pleased to be here today to discuss with the Subcommittee the Food and Drug Administration's (FDA) activities related to the unapproved new drug RU-486.

I am Ronald Chesemore, Associate Commissioner for Regulatory Affairs. I am accompanied by Dr. Solomon Sobel, Director of our Division of Metabolism and Endocrine Drug Products and Sandra Barnes of our General Counsel's office.

As you know, RU-486 is a drug that is approved in France for early abortion through a limited distribution system when used with one of two prostaglandins also approved in France. Studies have been conducted on the treatment uses of this drug including brain tumors, breast cancer, Cushing's syndrome, and other types of cancer. This drug is the subject of an import alert which means that if observed coming into the country either through the mail or with individual persons, it will be detained by FDA field personnel and U.S. Customs Service officials. I should make the distinction, however, that with respect to the importation of unapproved drugs, those drugs under an investigational new drug application (IND) can be imported for research purposes, but individuals cannot import an unapproved drug for personal use unless it meets certain criteria. In the case of RU-486, importation for research for any therapeutic use could occur if an approved IND exists.

New Drug Approval Process

Before discussing issues related to RU-486 in more detail, I would like to describe for the record the procedures by which a new drug is brought to the market in this country. As you know, under the provisions of the Federal Food, Drug, and Cosmetic Act, FDA has the responsibility to monitor the use of investigational new drugs by allowing clinical studies to proceed, if appropriate, and to review the scientific data supporting a marketing application.

In order to start testing of investigational drugs in humans, an Investigational New Drug application (IND) must be filed with FDA by the drug's sponsor, usually a drug firm. The IND must contain information adequate to demonstrate that it is reasonably safe to test the drug or drugs in human subjects, including drug composition, manufacturing controls data, the results of animal testing, information on the training and experience of investigators, and a plan for the clinical investigation. In addition, FDA requires that informed consent be obtained to protect the rights and safety of human subjects. The clinical protocol content of that informed consent document must be approved by a local ethics committee known as an Institutional Review Board.

3

Clinical testing under an IND to develop adequate data to approve drugs for general marketing, whether done by the pharmaceutical company, an academic institution, or the National Institutes of Health, is normally divided into three sequential phases. It is important to point out that FDA does not actually do the clinical testing of drugs before they are marketed. Pharmaceutical manufacturers, the National Institutes of Health, and other research institutions across the country carry out programs to identify, develop and test drugs. It is FDA's responsibility to review and analyze the results of the testing to determine ultimately if a drug is safe and effective for widespread marketing for use by the general public.

Phase 1 is the initial introduction of an investigational therapy into humans to determine safety. Phase 1 studies are intended to assess the safety of the drug with an emphasis on identifying toxicities associated with varying doses, and to determine how the drug is distributed and degraded by the body. Phase 1 studies often include fewer than 100 volunteers (patients) and may take as long as one to two years to complete.

The second phase of IND testing usually involves the first controlled clinical studies in patients to evaluate the effectiveness of the drug for a particular indication and to

determine common short-term side effects. Phase 2 studies typically involve a few hundred patients. After Phase 2 studies are completed, the drug's sponsor usually has learned much about the drug's safety and effectiveness, and larger studies involving several thousand patients are conducted as Phase 3 studies. These Phase 3 studies generally are intended to verify the initial study results in broader populations, and to collect enough information to support marketing approval.

Once Phase 3 testing is completed, the sponsor submits the test results to FDA in the form of a New Drug Application (NDA). FDA's medical officers, pharmacologists, chemists, and statisticians review the application in parallel to determine if the sponsor's data demonstrate that the drug is safe and effective for the claimed indication. In certain instances, a drug may be brought before an expert Advisory Committee to the FDA in order to seek their advise on a new product. If it is determined that safety and effectiveness have been demonstrated, the drug is approved for marketing for that indication.

The above describes our process for approving new drugs. However, an import alert does not impact this process.

5

Importation of Unapproved New Drugs

Strictly interpreted, the Federal Food, Drug, and Cosmetic Act prohibits the importation of any drug product that has not been approved for use in this country. However, FDA has for many years exercised its enforcement discretion to allow the importation of small amounts of drugs for the personal use of patients, provided they do not pose unreasonable or significant safety risks, and their use will not be commercialized. The intent of FDA's personal importation policy is to guide FDA field personnel on how to use enforcement discretion. FDA's personal importation policy is contained in the Pilot Guidance issued in July 1988 and in chapter 9-71 of FDA's Regulatory Procedures Manual. I would like to submit copies of these documents for the record.

Specifically, the policy provides that FDA will use its discretion to allow entry of certain unapproved drug products that are carried or mailed into this country if they meet the following criteria:

- the quantity of the drug or other product demonstrates that the product is intended for personal use - generally, not more than a 3-month supply for one person;

- the product is intended to treat a serious condition for

which no treatment is commercially available in this country;

- there is no known promotion or commercialization of the product;

- the product does not pose unreasonable safety risks to the patient; and

- the patient confirms that the product is for his or her personal use, and provides the name and address of a practicing physician who will be responsible for his or her treatment (or provides evidence that the product is needed to continue treatment begun in a foreign country).

On a case by case basis, the above criteria are considered in determining whether FDA will allow entry of certain unapproved drug products. It should be noted that discretion has also been used to allow importation of unapproved drugs where the intended use of the drug is appropriately identified, the use is not for treatment of a serious condition, and the drug is not known to represent a significant health risk. This is meant to apply, for example, to a traveller who develops an upper respiratory tract infection and reenters the United States with a remedy purchased abroad.

In those instances where the Agency has determined that importation of a drug product is not appropriate, it may advise its district offices by issuing an import alert. An import alert means that the discretion allowed under the personal importation policy is not appropriate and FDA field personnel are directed to detain and refuse entry of a certain product under specified circumstances. Currently, there are 58 import alerts covering various human drugs and classes of drugs.

FDA may choose to issue an import alert under certain circumstances including:

- the personal importation of a product that appears to create either a direct or indirect risk to the public health; or
- the promotion of unapproved foreign products; or
- the repeated importation of products that constitute a health fraud.

IMPORT ALERT ON RU-486

The approval and availability of RU-486 as an abortifacient

when used in conjunction with a prostaglandin in France has resulted in a great deal of publicity in this country. This has in turn generated a significant number of inquiries to the Agency from the public and the Congress about the status of RU-486 in the United States, and whether or not it should be imported into this country under our existing personal importation policy.

As you know, the use and distribution of RU-486 together with a prostaglandin in France are carefully controlled. The drugs are available only in certain clinics where patients can be closely monitored. Patients are required to make several trips to the clinic where RU-486 and the prostaglandin, an ancillary drug essential to the effectiveness of RU-486, are administered under the supervision of a physician. Once the patient receives RU-486, she is allowed to leave the clinic but must return 2 - 3 days later so that the she can receive the prostaglandin. After the patient is observed for several hours to determine that no complications have arisen, she is allowed to leave the clinic. The patient then must return to the clinic after several days for further observation.

Since neither RU-486 nor either of the two prostaglandins used in France is approved in this country, FDA has not evaluated their safety and effectiveness nor evaluated what controls might be appropriate in this country to ensure their safe use.

Although FDA can regulate the conditions of use for investigational drugs covered by an IND, no such controls would be in place to ensure safe use of these products if they were imported for personal use outside the IND procedures.

We, therefore, became concerned that the publicity regarding the availability of these drugs overseas might create a demand in this country, which could in turn foster importation of these unapproved drugs leading to unsupervised use and/or clandestine distribution. We recognize that importation may not be accomplished easily because of the limited availability of RU-486 in France. We believe, however, that it was appropriate to issue an import alert for these unapproved new drugs, given our responsibility to protect the public health. We also took this action because, as an abortifacient, RU-486 is not proposed for treatment of a serious condition for which no alternative treatment exists, a primary consideration in the development and implementation of our personal importation policy. Nor could the Agency conclude that RU-486 and the prostaglandins, as they might be used, posed no significant health risks. The Agency was concerned that because of the intended use of RU-486, potential users might well not be under the care a physician.

In addition, to be optimally effective, as I mentioned, RU-486 must be used in conjunction with a prostaglandin. Prostaglandins are potent drugs that themselves can cause serious adverse events. Indiscriminate or unsupervised use could be hazardous to the patient's health because of the risk of serious adverse effects such as excessive uterine bleeding, severe nausea, vomiting, and weakness, which might require prompt medical intervention.

Consequently, the import alert, which pointed out that use of RU-486 posed unacceptable safety risks to the American public, was issued on June 9, 1989, and alerted FDA field offices to detain all unapproved abortifacient drugs, including RU-486. I would also like to submit a copy of that alert for the record.

In summary, we continue to believe that use of our discretion to permit importation of unapproved RU-486 under the Agency's import policy is not appropriate. We believe that our decision to restrict the importation of RU-486 is sound from a public health standpoint and is consistent with our policy on personal importation of unapproved drugs.

We are aware of the American Medical Association's Resolution, adopted at its annual House of Delegates meeting in June 1990, supporting "the legal availability of RU-486 for appropriate research and, if indicated, clinical practice." In my

presentation, I described the process by which clinical research with RU-486 could proceed. We have placed no barriers in the way of research and can supply ample documentation of this fact to the Committee in executive session. It is, however, incumbent upon a sponsor to initiate the request to begin studies by submitting an application to FDA. The Agency is committed to maintaining the scientific integrity of FDA's new drug testing and approval process carried out under the existing laws enacted by the Congress.

We would be pleased to answer any questions you may have.

WPMAIL -ECHO
MAIL IMPORT-ALERT 'PILOT GUIDANCE FOR RELEASE'

DATE: JULY 20, 1988

FROM: DIRECTOR, OFFICE OF REGIONAL OPERATIONS (HFC-100)

SUBJ: "PILOT GUIDANCE FOR RELEASE OF MAIL IMPORTATIONS"

TO : REGIONAL FOOD AND DRUG DIRECTORS
DISTRICT DIRECTORS
IMPORT PROGRAM MANAGERS
COMPLIANCE BRANCH DIRECTORS
INVESTIGATIONS BRANCH DIRECTORS
LABORATORY BRANCH DIRECTORS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)

RICHARD SWANSON (HFC-160)
CHARLES EVERLINE (HFC-210)
ARTHUR LEVINE (GCF-1)
HOWARD PIPPIN (HFF-310)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
JACK HARTY (HFY-50)
BRUCE WILLIAMS (HFB-CANADA)
STERK LARSON (HFC-41)
SAMMIE YOUNG (HFD-301)

OFFICE OF ENFORCEMENT (HFC-200)
ERNEST BRISSON (HFC-230)
EDWARD STEELE (HFF-25)
OFFICE OF COMPLIANCE (HFF-300)
DANIEL MICHELS (HFD-300)
EDWARD BALLITCH (HFV-230)
WALTER GUNDAKER (HFZ-300)
WILLIAM B. CARTER (HFF-26)
BETTY CHISM (HFC-42)
THOMAS BOZZO (HFB-100)

******CORRECTED COPY******

NOTE: THIS GUIDANCE IS BEING ISSUED ON A PILOT BASIS AND IS SUBJECT TO CHANGE AND/OR CANCELLATION. IF THE PILOT PROVES SUCCESSFUL, WITH NO SIGNIFICANT PROBLEMS, CHAPTER 9-71 OF THE REGULATORY PROCEDURES MANUAL MAY BE APPROPRIATELY REVISED.

SUBJ: Pilot Guidance for Release of Mail Importations

Because of the desire to acquire articles for treatment of serious and life-threatening conditions like AIDS and cancer, individuals have been purchasing unapproved products from foreign sources. Some of these products

are sold over-the-counter in the country of origin while others are available from clinics where the purchaser was treated. Such products are often shipped to the purchaser by mail.

Even though such products are subject to refusal, we may use our discretion to examine the background, risk, and purpose of these products before making a final decision. To assure that the districts are operating in a uniform manner, the following guidance is provided for dealing with personal use shipments.

1. Except as modified by these instructions, established guidance found in RPM-9-71, exhibits X9-71-1 and X9-71-2 should be followed.

2. A product entered for personal use, which meets the criteria in item 4 below, may proceed without sampling or detention.

3. Products that are not identified, or are not accompanied by documentation of intended use, should be detained. Other reasons for detention may include: size of the shipment (amount inconsistent with personal use), fraudulent promotion or misrepresentation, or an unreasonable health risk due to either toxicity or possible contamination. In such cases, the appropppriate center should be contacted for guidance concerning release of the product.

4. Following detention, shipments may be released to an individual if the following criteria can be satisfied and there is no safety risk or evidence of fraud:

   - o the product was purchased for personal use
   - o the product is not for commercial distribution and the amount of product is not excessive (i.e., 3 months supply of a drug)
   - o the intended use of the product is appropiately identified
   - o the patient seeking to import the product affirms in writing that it is for the patient's own use and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product

5. If the district should encounter a situation suggesting promotional and/or commercial activity that falls within our health fraud guideline, the district should recommend that an Import Alert be issued for the automatic detention of the product and identification of the promoter involved.

6. The model letter currently in Exhibit X9-71-2 should be revised according to the attached during this pilot.

7. The article may then be RELEASED WITH COMMENT upon receipt of the letter as follows:

"The drug you have obtained for your personal use appears to be unapproved in the U.S. We understand you will use this limited quantity under medical supervision; however, future personal shipments may be refused entry if we learn, among other things, the drug presents an unreasonable risk or it has been commercially promoted to U.S. citizens."

The above guidance should be used as part of the current outstanding instructions for dealing with mail packages as found in Chapter 9-71 of the RPM.

/s/
Ronald G. Chesemore

WPMAIL -ECHO
MAIL IMPORT-ALERT 'IMPORT ALERT 66-47'

DATE: JUNE 6, 1989

FROM: DIRECTOR, DIVISION OF FIELD INVESTIGATIONS (HFC-130)

SUBJ: IMPORT ALERT #66-47 "Automatic Detention of Abortifacient Drugs"

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

ARVIN SHROFF (HFC-101)
INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)
OFFICE OF REGULATORY GUIDANCE (HFF-310)

RICHARD SWANSON (HFC-160)
CHARLES EVERLINE (HFC-210)
ARTHUR LEVINE (GCF-1)
OFFICE OF COMPLIANCE (HFF-300)
DANIEL MICHELS (HFD-300)
EDWARD BALLITCH (HFV-230)
WALTER GUNDAKER (HFZ-300)
FIELD PROGRAMS BRANCH (HFF-26)
BETTY CHISM (HFC-42)
THOMAS BOZZO (HFB-100)
JOHN WESSEL (HFC-6)
OFFICE OF ENFORCEMENT (HFC-200)
ERNEST BRISSON (HFC-230)
EDWARD STEELE (HFF-25)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
JACK HARTY (HFY-50)
BRUCE WILLIAMS (HPB-CANADA)
STERK LARSON (HFC-41)
SAMMIE YOUNG (HFD-301)
CATHERINE CARNEVALE (HFC-6)

* * * * CORRECTION TO PREVIOUS TRANSMISSION * * * *

* * * * NAME OF PRODUCT CHANGED TO RU486 * * * *

TYPE OF ALERT: Automatic Detention

PRODUCT : Abortifacient Drugs (drug that induces abortion)

PROBLEM : New Drug without NDA/Safety from unsupervised use (DRND/DRHL)

PRODUCT CODE : 66[][][][][][]

PAC : 56000H

COUNTRY : All

MANUFACTURER/
SHIPPER : ALL UNAPPROVED

CHARGE : "The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to be a new drug without an effective new drug application (NDA) as required by Section 505(a)."

RECOMMENDING
OFFICE : HFC-131 Import Operations Branch

REASON FOR
ALERT : Questions have been raised about a new abortifacient product, RU486 or "Mifepristone", (Import Bulletin 66-B13 9/26/88) and whether the agency should use its discretion, pursuant to the Pilot Guidance for Release of Mail Importations (7/20/88), or otherwise, to allow its importation for personal use. FDA has concluded that unapproved products of this kind would be inappropriate for release under the personal importation policy. The intended use of such drugs could pose a risk to the safety of the user.

INSTRUCTIONS : Automatically detain all shipments of unapproved abortifacient drugs.

FOI : No purging is required of this alert.

/s/
Robert C. Fish

FOOD AND DRUG ADMINISTRATION

REGULATORY PROCEDURES MANUAL

Transmittal No. 90-02 Date 12/11/89

MATERIAL TRANSMITTED

Part 9-71 - Coverage of Personal Importations
Exhibits X9-71-1 and X9-71-2

MANUAL MAINTENANCE

Remove	Insert
Part 9-71 including Exhibits X9-71-1 and X9-71-2 and Part 9-72 - TN 77-1 (04/01/77)	Part 9-71 including Exhibits X9-71-1 and X9-71-2

EXPLANATION OF CHANGES

Reissued to consolidate policy and procedures that previously existed in RPM Chapter 9-71, Mail Importations; RPM Chapter 9-72, Coverage of Importations Contained in Personal Baggage; and, Pilot Guidance for Release of Mail Importations.

Director, Division of Field Investigations
Office of Regional Operations
Office of Enforcement

DISTRIBUTION:

All Holders of the Regulatory Procedures Manual

CHAPTER 9-71 COVERAGE OF PERSONAL IMPORTATIONS

9-71-00 Purpose
10 Background
20 Personal Baggage
25 Mail Shipments
30 General Guidance
40 Import Alerts

9-71-00 PURPOSE

To provide guidelines for the coverage of personal-use quantities of FDA-regulated imported products in baggage and mail and to gain the greatest degree of public protection with allotted resources.

9-71-10 BACKGROUND

This new chapter consolidates policy and procedures that previously existed in RPM Chapter 9-71, Mail Importations; RPM Chapter 9-72, Coverage of Importations Contained in Personal Baggage; and, Pilot Guidance for Release of Mail Importations.

Because the amount of merchandise imported into the United States in personal shipments is normally small, both in size and value, comprehensive coverage of these imports is normally not justified. Small shipments, however, are occasionally entered in baggage or mail as a way of avoiding formal entry review. This guidance clarifies how FDA may best protect consumers with a reasonable expenditure of resources.

There has always been a market in the United States for some foreign made products that are not available domestically. For example, individuals of differing ethnic backgrounds sometimes prefer products from their homeland or products labeled in their native language to products available in the United States. Other individuals seek medical treatments that are not available in this country. Drugs are sometimes mailed to this country in response to a prescription-like order to allow continuation of a therapy initiated abroad. With increasing international travel and world trade, we can anticipate that more people will purchase products abroad that may not be approved, may be health frauds, or may be otherwise not legal for sale in the United States.

In addition, FDA must be alert to foreign and domestic businesses that ship unapproved, fraudulent, or otherwise illegal medical treatments into the United States or who encourage persons to order these

FORM FDA 3250 (5/88)

products. Such treatments may be promoted to individuals who believe that treatments available abroad will be effective in the treatment of serious conditions such as AIDS or cancer. Because some countries do not regulate or restrict the commercial exportation of unapproved products, people who mail order from these businesses may not be afforded the protection of either foreign or U.S. laws. In view of the potential scale of such commercial operations, FDA has focused its enforcement resources more on products that are shipped commercially, including small shipments sclicited by traditional mail-order promotions, and less on those products that are personally carried, shipped by a personal non-commercial representative of a consignee, or shipped from a foreign medical facility where a person has undergone treatment.

9-71-20 PERSONAL BAGGAGE

FDA personnel are not to examine personal baggage. This responsibility rests with the U.S. Customs Service. It is expected that a Customs officer will notify the local FDA district office by telephone when he or she has detected a promotional shipment or a shipment of an FDA-regulated article intended for commercial distribution (see 9-71-30), an article that FDA has specifically requested be detained, or an FDA-regulated article that represents a health fraud or an unknown risk to health.

When items in personal baggage are brought to FDA's attention, the district office should use its discretion, on a case-by-case basis, in accordance with the guidance provided in 9-71-30 in deciding whether to request a sample, detain the article, or take other appropriate action.

9-71-25 MAIL SHIPMENTS

Generally, FDA personnel only monitor mail importations. It is expected that a Customs officer from the Customs Mail Division will examine a parcel and will set it aside if it appears to contain a drug, biologic, or device, an article that FDA has specifically requested be detained, or an FDA-regulated article that represents a health fraud or unknown risk to health.

FDA should audit those parcels set aside by Customs in accordance with the guidance provided in 9-71-30 using the following procedures:

Complete the form FD-725 "Mail Collection Report" for each parcel collected for sampling. Generally, a physical sample is not required on mail importations because a documentary sample, e.g.,

labels, inserts, etc., will be sufficient for most regulatory purposes. If a physical sample is needed, collect only the minimum necessary for analysis by the laboratory. The remaining portion should not be removed from the custody of the Customs Mail Division.

Importations detained in accordance with this guidance should be held by Customs until they are either released or refused entry. Attached as guides are two specimen letters that may be sent with the Notice of Detention and Hearing when a parcel is detained: Exhibit X9-71-1 for use in general mail importations, and Exhibit X9-71-2 for use in unapproved drug or device mail importations.

On occasion, products detained by FDA will be mixed with non-FDA-regulated products. When we refuse admission of the FDA-regulated portion, any request for the release of the non-FDA-regulated portion should be referred to the Customs Mail Division with a Notice of Refusal of Admission covering the detained article. Final disposition of all merchandise, including the destruction of detained merchandise, is the responsibility of Customs.

9-71-30 GENERAL GUIDANCE

Even though all products that appear to be in violation of statutes administered by FDA are subject to refusal, FDA personnel may use their discretion to examine the background, risk, and purpose of the products before making a final decision. Although FDA may use its enforcement discretion to allow admission of certain violative items, this should not be interpreted as a license to individuals to bring in such shipments.

A. Commercial or Promotional Shipments

Commercial and promotional shipments are not subject to this guidance. Whether or not a shipment is commercial or promotional should be determined by a number of factors including the type of product, the accompanying literature, the size, value, and the destination of the shipment. FDA personnel should also consider whether an importation of drugs or medical devices is a commercial shipment by evaluating whether the article appears to have been purchased for personal use or whether the quantity suggests commercial distribution (i.e., the supply exceeds what one person might take in approximately three months). Commercial shipments include most shipments other than those products that are personally carried, shipped by a personal non-commercial

representative of a consignee, or shipped from a foreign medical facility where a person has undergone treatment.

B. Products Other than Drugs and Devices

Many products other than drugs, biologics, and devices that individuals seek to import in personal quantities do not pose a significant health risk, although they appear to be violative and may already be the subject of an import alert or automatic detention on the basis of filth or labeling problems. When such items are brought to FDA's attention by Customs, it may be appropriate for FDA personnel to use their discretion to "Release with Comment" and advise the importer of the agency's concerns. FDA personnel should be alert to, and should detain, however, those products that do pose a significant health risk, such as ackee or betel nuts.

C. Drugs, Biologics, and Devices

When personal shipments of drugs and devices that appear violative are brought to FDA's attention by Customs, FDA personnel will have to use their discretion to decide on a case by case basis whether to sample or detain. Generally, drugs and devices subject to Import Alerts are not amenable to this guidance. Devices to be used by practitioners for treating patients should not be viewed as personal importations subject to this chapter. Drugs subject to Drug Enforcement (DEA) jurisdiction should be returned to Customs for handling.

In deciding whether to exercise discretion to allow personal shipments of drug or devices, FDA personnel should consider a more permissive policy in the following situations:

- o when the intended use is appropriately identified, such use is not for treatment of a serious condition, and the product is not known to represent a significant health risk; or

- o when 1) the intended use is unapproved and for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means; 2) there is no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue; 3) the product is considered not to represent an unreasonable risk; and 4) the individual seeking to import the product affirms in writing that it is for the patient's own use (generally not more than 3 month supply)

and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product or provides evidence that the product is for the continuation of a treatment begun in a foreign country.

Where there are any questions about the application of these factors to any product, the product should be detained and FDA personnel should consult with the appropriate headquarters office.

Where a shipment is not detained or refused, FDA personnel should "Release with Comment" and, as appropriate, advise the recipient that 1) the drug (or device) that has been obtained for personal use appears to be unapproved in the United States; 2) the drug (or device) should be used under medical supervision; 3) FDA may detain future shipments of this product; and 4) the patient's physician should consider enrolling the patient in an Investigational study or applying for an Investigational New Drug (IND) exemption.

9-71-40 IMPORT ALERTS

FDA personnel should recommend to HFC-131 the issuance of an import alert if they encounter:

- o personal importation of products that represent either a direct or indirect risk;
- o the promotion of unapproved foreign products for mail-order shipment; or
- o repeated importation of products that represent a health fraud.

MODEL LETTER FOR USE IN GENERAL MAIL IMPORTATIONS

(LETTERHEAD)

A mail shipment of an article from a foreign country addressed to you is being detained at the U.S. Post Office. All products of this kind must meet the requirements of the Federal, Food, Drug, and Cosmetic Act or other laws enforced by the U.S. Food and Drug Administration. These laws are designed to protect you from, among other things, unsafe or misrepresented foods, drugs, biologics, cosmetics, devices, and other articles. The product addressed to you does not appear to comply with the law.

Please read the enclosed Notice of Detention and Hearing carefully since it explains why FDA believes that the product sent to you is in violation. The Notice does not in any manner accuse you of violating any law.

If you have a good reason to believe that the product does comply with the law and wish to discuss it with us, you may come personally to this office or write to us within the time limit shown on the Notice.

If you do not wish to claim this shipment, you may disregard the Notice and the shipment will be returned to the sender without cost to you. The shipment will be returned automatically if we do not hear from you within the time limit shown on the Notice.

Sincerely yours,

Enclosure:

MODEL LETTER FOR USE IN DETENTIONS OF DRUGS AND DEVICES

(LETTERHEAD)

A mail shipment addressed to you of a drug from a foreign country is being detained at the U.S. Post Office. All products of this kind must meet the requirements of the Federal Food, Drug, and Cosmetic Act, which is designed to protect you from products that have not been shown to be safe and effective and that are not labeled in a truthful, accurate, and non-misleading manner.

Please read the enclosed Notice of Detention and hearing carefully, since it explains why the product addressed to you appears to violate U.S. law. The Notice does not accuse you in any manner or violating any law.

If the drug is not approved for distribution in the United States, FDA may consider releasing the product to you for your own personal use if you provide a statement containing:

- o adequate documentation that the product is for your own use and for treatment of a serious condition, and include the name and address of the doctor licensed to practice in the United States who is responsible for your treatment with this product; or

- o adequate documentation that the product is for the continuation of a treatment of a serious condition begun in a foreign country.

Send this statement to this office and we will promptly review your submission and consider release of the product.

If you have good reason to believe that the product does comply with the law and you wish to discuss it with us, you may come personally to this office or write to us within the time limit shown on the Notice.

If you do not wish to claim this shipment, you may disregard the Notice and the shipment will be returned to the sender without cost to you. The shipment will be returned automatically if we do not hear from you within the time limit shown on the Notice.

Sincerely yours,

Enclosure:

• U.S. GOVERNMENT PRINTING OFFICE:1989-261-198:27210

DEPARTMENT OF HEALTH & HUMAN SERVICES

Jeane Mauro '90
Public Health Service

Memorandum

p 1, 4

Date March 10, 1990

From Acting Commissioner of Food and Drugs

Subject RU-486

To Assistant Secretary for Health

EXHIBIT A

This will provide you with further information on the RU-486 import alert, which was the subject of a February 17 Washington Post editorial. This editorial failed to mention that FDA has issued import alerts for many other drug products, posing both lesser and greater safety risks than RU-486, and thus created the inaccurate impression that FDA has singled out RU-486 for alleged political reasons. FDA has in fact many standing import alerts for other drug products--compound Q and dextran sulfate, for example--as well as certain food products and medical devices that are known to present a range of safety problems.

Strictly interpreted, the law prohibits the import of any product that is unapproved for use in this country. However, in response to requests from desperately ill patients and their representatives, FDA has for many years exercized its discretion to allow the importation of small amounts of drugs and other products to be imported for personal use, provided they do not pose significant or unreasonable safety risks, and are not commercialized.

The RU-486 import alert, which has been in effect since last summer, was based on a conclusion that the RU-486 regimen, which includes a prostaglandin (also unapproved for use in this country) could present an unreasonable safety risk due to the fact that its intended use makes it likely that it would be used without benefit of supervision of a physician, and that indiscriminate or unsupervised use could be hazardous to health. Because RU-486 is not proposed for treatment of a serious (life-threatening) condition, yet poses a safety risk, FDA did not regard the drug as a proper candidate for importation under the agency's personal importation policy. Moreover, the media publicity in this country regarding the availability of RU-486 overseas raised for FDA the possibility that a demand would be created in this country which in turn would foster importation of the drug for commercial reasons.

EVOLUTION OF REGULATORY PROCEDURES
REGARDING PERSONAL IMPORTATIONS

4/1/54 - Memorandum from Division of Field Operations to Chiefs of Districts

This memo transmitted policy to the effect that our attention should be confined to those private mail importations which are dangerous to health, grossly false and misleading in their labeling, or are violative and appear to be part of a mail order business. This policy was not substantially different from current policy.

4/1/77 - Chapter 9-71 "Mail Importations"

(12)

Provided detention for all unapproved drugs regardless of quantity but limited field coverage of mail entries. Certain shipments could be released after detention on request of personal physician.

4/1/77 - Chapter 9-72 "Coverage of Importations contained in Personal Baggage"

Provided discretionary entry of small quantities of unapproved drugs contained in personal baggage if the drugs were not known hazards or subject of an import alert.

7/20/88 - "Pilot Guidance for Release of Mail Importations"

This pilot guidance supplemented the guidance in Chapters 9-71 and 9-72 above and gave more explicit criteria for release of personal mail importations.

9/16/88 - Letters issued by Dr. Young to AMA, PMA, IOM

These letters explained that the pilot guidance was part of "an ongoing effort to clarify and simplify FDA's handling of small, personal quantities of unapproved drugs" in import status.

12/11/89- Chapter 9-71 (revised) "Coverage of Personal Importations"

Combined the two chapters issued in 1977 and provided more detailed guidance. Also provided for discretionary entry of up to a 3 month supply of unapproved drugs not known to be a health hazard, not subject of an import alert and/or not commercialized in U.S.

46 p2

Page 2 - Assistant Secretary for Health

I am attaching a chronology of the evolution of FDA's longstanding personal importation policy from its initial statement in 1954 until the present. Instructions to FDA compliance personnel, which were recently modified to clarify this policy, provide that FDA field officers have discretion to release a small supply of unapproved, imported drugs in the following situations:

- when the drug is for a serious condition for which treatment is otherwise not available, and the risk posed by the drug is not unreasonable;
- there is no known commercialization of the drug.

(The guidance also provides for discretionary release of drugs that meet FDA criteria for over-the-counter marketing status and do not pose a serious health risk.)

I am told by FDA staff that as of January 12, no actual detention of RU-486 could be identified in the Import Detention System's national detention file. In addition, FDA's Import Operations Branch is not aware of any detention of the drug, either as a result of the FDA import alert, or based on Department of Customs regulations (of which we recently became aware) that require detention of any drug clearly intended for inducing abortion.

At this time, FDA has some individual-investigator INDs for RU-486 for an abortifacient indication, as well one from the Population Council, which is considered to be public information and which has been ongoing for several years. I understand from staff of the Center for Drug Evaluation and Research that there has been no recent information submitted on the individual-investigator INDs and that none of the studies for the INDs have reached Phase 2. The Population Council's studies, which were conducted in Los Angeles (161 patients), Paris, and Uppsala, have been completed, and the Council informs us that they have no new studies planned at this time. There are RU-486 INDs for other indications, including an active NIH IND to study biochemical parameters.

There are no pending NDAs for RU-486. I am told by CDER staff that the European manufacturer of RU-486, Roussel Uclaf, is not interested in entering the U.S. market at this time. (The issue is somewhat complicated by the fact that neither of the prostaglandins approved for use with RU-486 in France are marketed in this country, and they are not manufactured by Roussel Uclaf). As we discussed, FDA will handle any application for RU-486 in the same way as an application for any other drug, and our review will be based on an impartial evaluation of the scientific data.

a. SUBJECT OF ISSUANCE	Automatic detention of abortifacient drugs Import Alert # 66-		6
b. PREPARED BY	c. NAME AND ORGANIZATION Marvin Blumberg Import Operations HFC 131	d. BUILDING AND ROOM NO. PHLN 12-18	e. PHONE NO. 443- 8553

f. PURPOSE (Changes in policy or procedures, instructions or forms cancelled, revised or created)

Do to numerous enquiries to OLA/HFC-1/FOD and districts on suitability for entry of abortifacient (RU846) drugs under the Pilot Guidance for Release of Mail Importation for personal use, this import alert establishes the agency's position on this question. The alert establishes that this product is not to be released under the pilot guide and that the product is not suitable for personal use without proper supervision by a physician.

g. ORIGINATING OFFICE CLEARANCE	h. TYPED NAME, TITLE AND ORGANIZATION	i. SIGNATURE	j. DATE SIGNED
	MARVIN BLUMBERG HFC-131 FOD	Marvin Blumberg	3/31/89

k. CLEARANCE ROUTING

☐ SEQUENCE CLEARANCE (One shall in notice, complete action and forward in _____ work days.) ☐ CONCURRENT CLEARANCE (Copy to each clearance pole, complete action and return by _____.)

ROUTING SYMBOL	SIGN UNDER APPROPRIATE COLUMN			CLEARANCE DATE
	CONCUR	CONCUR (Recommended change(s) attached)	DO NOT CONCUR (Reasons attached)	
HFC-2				
HFD-300		for Dennis Gleaf		5/25/89
HFC-1				
HFC-132				
HFC-100				

EXHIBIT B

Form FD 1306 (6/78)

COMMISSIONER / DEPUTY CORRESPONDENCE — FDA

Referral Date 4/7/89

SUBJECT: Requests info re importation policy re RU486

INCOMING FROM: Senator Jesse Helms

DETAILED REVIEW 1 | SUMMARY REVIEW 2 | PROCEDURAL REVIEW 3 (Circle One)

REVIEWED BY: Reviewer	Date	OFFICE OF THE COMMISSIONER Reviewer	Date
J. Alstad	3/17/89	Mr. Navazio, HF-40	
W. Schwemer	3/30/89	Mr. Levitt, HF-9	
J. Levitt	4/10/89		
K. Cannon	4/14/89	Mr. Benson, HF-2	
		Dr. Young, HF-1	

Correspondence Monitor: Marie Dromerick TRAC #: 890564

COMMISSIONER & DEPUTY'S COMMENTS / ASSIGNMENTS

EXHIBIT C

The Honorable Jesse Helms
United States Senate
Washington, D.C. 20510

Dear Senator Helms:

This is in further response to your February 23, 1989, inquiry relating to the Food and Drug Administration's (FDA) policy on the importation of unapproved drugs into the United States. Specifically, you asked whether citizens and companies would be allowed to import the drug RU-486 (mifeprisone), which is not approved for marketing in the United States.

For many years FDA has, as a matter of discretion, permitted individuals to bring into the United States, for their personal use, quantities of drugs sold abroad but not approved in the United States. Personal use quantities are generally considered to be amounts for a patient's treatment for three months or less. Imports involving larger quantities are generally not permitted as they lead themselves to commercialization.

As you know, in July 1988, the Agency issued written guidance to our field offices to clarify the policy's applicability to mail imports, and to ensure that our policies and practices in this important area are consistent throughout the country. It states that unapproved drugs may be imported if there is no unreasonable safety risk or evidence of fraud, and other criteria are met relating to personal use, quantity, etc.

We do not believe that this policy can be appropriately applied to the importation of RU-486 in that use of the product could present an unreasonable safety risk. The intended use of this drug makes it likely it would be used without benefit of supervision of a physician and indiscriminate or unsupervised use could be hazardous to the patient's health. For example, side effects of the drug include uterine bleeding, severe nausea, vomiting, and weakness which might require prompt medical intervention could occur. Copies of our July 20, 1988 guidance and an import bulletin on RU-486 dated September 26, 1988 is enclosed for your information.

I hope this information is helpful. If I can be of any further assistance, please do not hesitate to contact me.

Sincerely yours,

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Dear Correspondent:

This is in reply to your recent letter concerning RU-486, an abortifacient recently approved in France.

RU-486 has not received FDA approval for marketing, although this drug is in clinical trials.

The Food and Drug Administration reviews drugs but does not test them. Drug sponsors, generally manufacturers, arrange for testing by experts, as well as shouldering the cost, and include the results in new drug applications.

Before we will permit testing a drug in humans, the sponsor of the drug must provide us with information demonstrating that the drug is reasonably safe to administer to humans. The sponsor must also provide manufacturing and control data, a detailed protocol of study, and names and qualifications of investigators who will be performing the clinical trials. These requirements were met by the Population Council, New York, New York.

The Federal Food, Drug, and Cosmetic Act, which we administer, sets forth the criteria for approval of new drugs. Approval is based on submission of data collected during the course of an investigation which demonstrates the drug is safe and effective for the purpose of use.

EXHIBIT D

Ethical concerns similar to yours have been expressed by others. We appreciate these concerns and respect your personal opinion. However, we hope that you will understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such action are submitted to the agency.

It is too early to comment whether this drug will be safe and effective for any conditions under study.

Sincerely yours,

cc:
HFA-224
HFD-365/C
HFD-360/RF
DWalker:11/28/88
Init:PJSavino:/89
F/T:dh:8/11/89:Doc #0224w

NOV. 28, '88

Diane F. Walker
Consumer Safety Officer
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Congress of the United States
House of Representatives

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May 5, 1989

Honorable Frank Young, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Young:

An article published in the December 1988 issue of American Health, entitled "Mail Order Drugs from Abroad," asserts that you have approved a policy that would allow American citizens to mail order non-approved drugs from overseas for personal use.

EXHIBIT E

While this apparent blanket policy is prima facie disturbing overall, one specific concern is that the French abortifacient RU 486 is not one of the 40 drugs specifically excluded. We are aware of the September 26, 1988 memo signed by Burton I. Love but we have seen no official statement from you confirming the ban on RU 486.

The U.S. government should not be involved in abetting abortion. This includes regulations that would allow the use of abortifacients such as RU 486. But of equal importance, the FDA should look at the effects non-approved drugs may have on the health and welfare of U.S. citizens. RU 486 has more than a dozen "contra indications" which proscribe its use. If a woman does not meet certain criteria, than she risks serious complications. That is why in France and China, where it has been legalized, RU 486 can only be administered under direct medical supervision. How then could the FDA possibly allow it to be purchased through mail order?!

We would greatly appreciate a clarification on your policy. Does your policy directive allow the importation of RU-486 or similar non-approved abortifacient drugs? If it does, have abortifacients such as RU 486 been imported under your directive? Finally, are there regulations currently being drafted that would add abortifacients, and specifically RU 486, to the list of prohibited drugs?

We look forward to your prompt reply.

Sincerely,

Robert K. Dornan, M.C. Henry Hyde, M.C. John LaFalce, M.C.

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Regulatory Procedures Manual
Part 9, Imports
Chapter 9-79

IMPORT ALERT	ORO/DFI (HFC-131) IMPORT OPERATIONS
AUTO DETENTION OF ABORTIFACIENT DRUGS	No.: 66-47 Date: June 6, 1989

TYPE OF ALERT: Automatic Detention

PRODUCT : Abortifacient Drugs (drug that induces abortion)

PROBLEM : New Drug without NDA/Safety from unsupervised use (DRND/DRHL)

PRODUCT CODE : 66[][][][][][]

PAC :

COUNTRY : All

MANUFACTURER/
SHIPPER : ALL UNAPPROVED

CHARGE : "The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to be a new drug without an effective new drug application (NDA) as required by Section 505(a)."

RECOMMENDING
OFFICE : HFC-131 Import Operations Branch

REASON FOR
ALERT : Questions have been raised about a new abortifacient product, RU486 or "Mifepristone", (Import Bulletin 66-813 9/26/88) and whether the agency should use its discretion, pursuant to the Pilot Guidance for Release of Mail Importations (7/20/88), or otherwise, to allow its importation for personal use. FDA has concluded that unapproved products of this kind would be inappropriate for release under the personal importation policy. The intended use of such drugs could pose a risk to the safety of the user.

EXHIBIT F

INSTRUCTIONS : Automatically detain all shipments of unapproved abortifacient drugs.

[illegible] : No purging is required of this alert.

SCIENTISTS, ACADEMICIANS AND HEALTH PROFESSIONALS FOR RU486

TO: EDOUARD SAKIZ
Roussel Uclaf
Paris, France

WOLFGANG HILGER
Hoechst, A.G.
Frankfurt, West Germany

CEOs
American Pharmaceutical
Corporations

WHEREAS ... Millions and millions of women will benefit from the development and dissemination of RU 486 — a safe, effective way to terminate a pregnancy through the first 49 days, which will greatly reduce the need for surgical abortion; and

WHEREAS ... RU 486 is an effective treatment for Cushing's Syndrome and a potential treatment for some types of breast cancer, meningioma, endometriosis, and difficult deliveries; and

WHEREAS ... Roussel holds the patent on RU 486 and can license distribution of this crucial drug in the United States; and

WHEREAS ... With threats of economic reprisal, opponents of abortion have hindered the research, development and distribution of this important medical advancement; and

WHEREAS ... The vast majority of Americans — who support RU 486 and expanded contraceptive research and development — have been silent up to now;

THEREFORE ... I want you to know that Roussel, Hoechst, A.G., and American pharmaceutical corporations have my full support for marketing RU 486. I will do everything that I can do to bring RU 486 into the United States.

Signature	Name (please print)
Title/Department	Street Address
Institution/Organization	City, State, Zip
Telephone	Date

HELP MAKE RU 486 AVAILABLE TO AMERICAN WOMEN

Please return to: Feminist Majority Foundation
186 South Street
Boston, Massachusetts 02111
(617) 695-9688; Fax (617) 695-9747

FEMINIST MAJORITY FOUNDATION

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
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APR 10 1986

The Honorable Gordon J. Humphrey
United States Senate
Washington, D.C. 20510

Dear Senator Humphrey:

Thank you for your recent letters, to Dr. Wyngaarden, Surgeon General Koop and to me, regarding the use of Federal funds for research on the compound RU 486.

Following my meeting with representatives of the pro-life movement on January 22, Dr. Wyngaarden, Dr. Koop, Dr. Donald Ian Macdonald (the Acting Assistant Secretary for Health) and I investigated the use by the National Institutes of Health (NIH) of HHS funds to support research on RU 486.

Enclosed is a comprehensive report on research supported or conducted by the NIH involving this compound. The identified NIH research involving RU 486 includes projects related to breast cancer, lymphoma, glaucoma, Cushing's Syndrome, basic reproductive biology, and its potential use as a contraceptive. After carefully reviewing each of these projects, and confirmation by telephone with the principal investigators, we are confident that none of this research was on the use of RU 486 as an abortifacient. The NIH has scrupulously adhered to congressional directives, departmental regulations, and Administration policy, and has neither supported nor conducted abortifacient research involving RU 486, or any other drugs or devices.

The drug RU 486 was developed in France approximately six years ago. It has two types of actions:

- It is an antiglucocorticoid, and so blocks effects of adrenal hormones such as cortisone. This action makes it useful for physiologic studies, because it can block glucocorticoid activity to help us understand the normal role of glucocorticoids in the body. It has also already had diagnostic and therapeutic applications at the NIH, with spectacular success in treating patients with Cushing's Syndrome, a disease caused by excess cortisone production. This action is also being studied for potential use in treating glaucoma and decreasing immune suppression in Acquired Immune Deficiency Syndrome (AIDS).

- RU 486 has an antiprogesterone action. Investigators at the NIH and elsewhere are using this property of the drug to study the normal role of progesterone in reproductive function, as well as its potential use as a contraceptive and as a treatment for some reproductive disorders such as endometriosis. Because of its antiprogesterone action, another extremely important potential use of RU 486 that is being studied by NIH is in the treatment of breast cancers that are progesterone responsive.

We are aware that abortifacient research utilizing RU 486 is being conducted. Because of its antiprogesterone effect, RU 486 is one of a number of drugs being studied in Europe, Asia, and in the United States as a potential drug for the termination of first trimester pregnancy. These drugs also are being tested for conditions unrelated to abortion. None of this abortifacient research receives support from the NIH.

The information in the enclosed report was gathered from all NIH Bureaus, Institutes, and Divisions. As you requested, the information includes the number, title, and a summary of each project; the name, institution, location, and phone number of the project's principal investigator; the funds the project received each year it was funded; publications resulting from the research; and other NIH documents on these projects, including applications or protocols, review documents, and progress reports. To assist you, we have prepared a brief summary of each of the identified NIH projects involving RU 486, and attached the requested documents under a separate tab for each of the projects.

The information you requested on RU 486 testing by private organizations cannot be so readily provided. As the Food and Drug Administration informed you in their response (copy enclosed) to your January 23 letter to them, information about applications to FDA to either test or approve a new drug is, by law, confidential data that cannot be released. FDA did confirm in their response that The Population Council had received permission to test RU 486 as an abortifacient, because the Council had met the legal requirements for conducting clinical tests of a new drug on humans. FDA was able to discuss that particular testing only to the extent that The Population Council had disclosed details in a published journal article. Thus, we cannot comply further with your request for information on non-Federally sponsored testing of this drug.

In view of the many potentially beneficial health uses of RU 486, I believe that it would be in the best interest of the American people to continue the HHS-funded studies on that compound. I can, however, assure you that no HHS funds have been used to support research on RU 486 as an abortifacient. Nevertheless, due to the considerable concern about the potential use of RU 486 as an abortifacient, I have asked the Director of the National Institutes of Health to continue monitoring closely this biomedical research to assure that no support will be provided to RU 486 as an abortifacient.

A similar reply is being sent to Senators Jesse Helms, John East, Charles Grassley, Steve Symms, and Jeremiah Denton.

Sincerely,

Otis R. Bowen, M.D.
Secretary

Enclosures

February 28, 1990

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U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Benson:

I would appreciate you sending the documents which my staff requested earlier today, when they visited your Rockville offices.

In addition, I would like the following information, which was not accessible to my staff at that time:

1) A list of any and all abortifacients which have been approved by the FDA.

2) Copies of all correspondence from your field offices regarding RU 486.

3) Copies of all correspondence between the FDA and U.S. Customs regarding RU 486.

Your prompt attention to this matter is deeply appreciated.

With warm regards,

Sincerely,

Ron Wyden

RON WYDEN
Chairman

RW/gab

cc: Hugh C. Cannon

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 02 1990

The Honorable Ron Wyden
Chairman, Subcommittee on Regulation,
Business Opportunities, and Energy
Committee on Small Business
House of Representatives
Washington, D.C. 20515

Dear Mr. Wyden:

This is in further response to your February 28, 1990 request for documents related to RU-486.

As you requested, we have enclosed a list of the Food and Drug Administration's (FDA) Approved Uterine-Acting Drugs (abortifacients). We have also included copies of FDA advisory committee meetings in 1978 and 1980 which contains discussions of estrogen for post-coital contraception; a May 1973 FDA Drug Bulletin discussing post-coital contraceptive use of DES; and a January 1975 Federal Register notice about labeling of DES for that use. We have not been able to identify any correspondence or other documents from the field or between FDA and United States Customs regarding RU-486.

For your information, we have also enclosed a Memorandum to the Assistant Secretary of Health from the Acting Commissioner regarding RU-486 dated March 10, 1990.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

Enclosures

MAJORITY MEMBERS
RON WYDEN, OREGON
CHAIRMAN

ELIOT L. ENGEL, NEW YORK
JIM OLIN, VIRGINIA
MICHAEL A. ANDREWS, NEW YORK

101ST Congress

United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Energy
B-363 Rayburn House Office Building
Washington, DC 20515

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STEVE JOHNSON
SUBCOMMITTEE STAFF DIRECTOR
202-225-7280

ANDREW POWELL
MINORITY SUBCOMMITTEE PROFESSIONAL
STAFF MEMBER
202-225-9125

May 24, 1990

James A. Benson
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Benson:

The Subcommittee is reviewing FDA's issuance of the June 9, 1989, automatic detention import alert on RU 486. I am concerned that the FDA has taken the position that this alert is justifiable on the grounds of health and safety risks. After reviewing many FDA documents relating to this decision, I cannot find specific documentation in FDA records attesting to the health and safety risks of RU 486.

In fact, the FDA has issued inconsistent, contradictory statements with respect to RU 486. For example, the agency states in its July 20, 1988 Pilot Guidance for Release of Mail Importations that any unapproved drug -- including RU 486 -- may be released to a patient, if the patient affirms in writing that it is for their "own use and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product."

Yet, June 9, 1989, the Agency appears to take a different position on RU 486. In a letter to Rep. Robert Dornan, Dr. Frank Young simply assumes that patients will use RU 486 without physician supervision -- and cites this assumption as creating a health and safety problem which is grounds for barring its use.

The only criteria the the FDA has used in finding RU 486 unsafe, is that it would be used without physician supervision. It does not appear from a review of FDA's files that the Agency has any evidence indicating that RU 486 would, in fact, be used without such supervision.

The FDA is treating RU 486 differently than other unapproved drugs, without any evidence that this treatment is warranted. The FDA appears to have tossed aside its physician supervision requirement for unapproved drugs, so that it can block physician supervised personal use of RU 486.

Additionally, in a memo to you from your chief counsel,

Margaret Jane Porter dated February 23, 1990, Ms. Porter indicates that "...because of the number of inquiries that the districts had received regarding its "legal status" in the United States, an import alert was required to clarify that the product was unapproved and, as such, was prohibited." Additional documents on file buttress this point. The handwritten cover page of the clearance record on the import alert, written by Marvin Blumberg, reads:

"Do [sic] to numerous inquiries to OLA/HFC-1/IOB and districts on suitability for entry of abortifacient (RU 486) drugs under the Pilot Guidance for Release of Mail Importation for personal use, this import alert establishes the agency's position on this question. The alert establishes the agencies that this product is not to be released under the pilot guide and the product is not suitable for personal use without proper supervision by a physician."

However, in a letter from your Associate Commissioner for Legislative Affairs, Hugh Cannon, dated April 3, 1990, Mr. Cannon notes that "We have not been able to identify any correspondence or other documents from the field...regarding RU-486."

On the basis of my staff's review of FDA's policies on RU 486, I would like to ask the following questions:

1) What evidence has the FDA gathered that indicates that RU 486 will be used without physician supervision?

2) Why has the FDA not applied its physician supervision requirement to RU 486 when it might ensure that RU 486 would be used safely?

3) Why has the FDA issued an import alert based upon inquiries from the field that have not been made?

4) What is the evidence of health or scientific risk that the Agency specifically used to issue the import alert for RU 486?

I would appreciate a prompt, written response to the above questions by June 22, 1990.

Sincerely,

Ron Wyden

RON WYDEN
Chairman

RW/gab

RON WYDEN, Oregon
CHAIRMAN

101st Congress

United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Energy
B-363 Rayburn House Office Building
Washington, DC 20515

RECEIVED
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HOUSE EXECUTIVE SECRETARIAT

September 19, 1990

Mr. William Raub
Acting Director
National Institutes of Health
Room 126, Building 1
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Mr. Raub:

The Small Business Subcommittee on Regulation, Business Opportunities and Energy, which I chair, has had a continuing interest in the government regulation or restriction of technologies, including pharmaceuticals, and the impact of such restriction and regulation on the competitiveness of U.S. small businesses.

As chairman of this subcommittee, and as an active member of the Energy and Commerce Committee's principal health issues subcommittee, I am particularly interested in this question of technology access as it involves or effects the drug RU 486.

In order to assist the subcommittee in its inquiry, I request that you provide the following information within 30 calendar days:

-- A description of any and all research undertaken by the NIH, its contractors or grantees involving RU 486.

-- A description of conclusions and possible policy decisions made by the NIH, or the Department of Health & Human Services, based on the research conducted under the auspices of the U.S. government, or the patronage of any other entity, foreign or domestic.

-- Your conclusions, or the conclusions of the U.S. Surgeon General and the Secretary of Health & Human Services, regarding the effectiveness of RU 486 for pharmacological and therapeutic treatments of diseases and adverse medical conditions.

-- A description of planned research, through the NIH, its contractors or its grantees involving RU 486.

Should you have any questions regarding the subcommittee's work, or these specific requests, please contact Steve Jenning of the subcommittee staff at (202) 225-7797.

Thank you for your assistance in this matter. I look forward to your response.

Sincerely,

RON WYDEN
Chairman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
Building : Shannon
Room : 126
(301) 496- 2433

NOV 16 1990

The Honorable Ron Wyden
Chairman, Subcommittee on Regulation,
Business Opportunities, and Energy
Committee on Small Business
U.S. House of Representatives
Room B-363 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Wyden:

In response to your letter of September 19, I am pleased to provide you with the enclosed report on research involving the drug RU 486 conducted or supported by the National Institutes of Health (NIH). The report includes current NIH research involving RU 486, as well as several projects which have recently been completed.

The policy of the NIH and the Department of Health and Human Services (HHS) regarding research involving RU 486 is twofold: 1) to conduct and support promising RU 486 research on potential uses of the drug which do not involve its action as an abortifacient, and 2) not to conduct or support any research on the abortifacient action of this compound. This policy, elucidated by the then Secretary of HHS, Dr. Otis Bowen, in his April 10, 1986, letter to several members of the U.S. Senate, states that "In view of the many potentially beneficial health uses of RU 486, I believe that it would be in the best interest of the American people to continue the HHS-funded studies on that compound. I can, however, assure you that no HHS funds have been used to support research on RU 486 as an abortifacient." This remains the policy of HHS and the NIH.

The RU 486 research being conducted and supported by the NIH continues to be most promising. Because much of this research is in progress, it is not possible to reach any scientific conclusions other than that, based on preliminary results, the continuation of this research holds significant promise for developing therapies and treatments for the various diseases, disorders, and conditions being studied. One example of a completed study is the initial clinical research on the use of RU 486 as a treatment for Cushing's Syndrome, which was recently concluded by NIH intramural scientists.

For many people with this devastating and potentially fatal disease, none of the previous treatment methods were successful. This preliminary research was quite successful, and essentially proved the value of RU 486 as a treatment to alleviate the symptoms of Cushing's Syndrome, as described in the enclosed report. In the foreseeable future, the NIH plans to continue to support and conduct the active research identified in the enclosed report.

Sincerely yours,

William F. Raub

William F. Raub, Ph.D.
Acting Director

Enclosure

October 1990

SUMMARY OF NIH RESEARCH PROJECTS INVOLVING RU 486

NATIONAL CANCER INSTITUTE

Research involving RU 486 supported by the National Cancer Institute (NCI) is continuing to exploit the antiprogesterone properties of the drug. Some breast cancers are stimulated to grow by estrogen. A major recent advance in breast cancer chemotherapy has been the use of the drug Tamoxifen to block the action of estrogen, removing the stimulus for the tumor to grow. Other breast cancers are stimulated by progesterone. Hopeful that RU 486 might have a role in these tumors comparable to that of Tamoxifen in estrogen-sensitive tumors, scientists are conducting research with RU 486 to test this possibility.

RO1 CA51482 Progesterone Receptor Regulation

Katzenellenbogen, Benita S. University of Illinois Urbana-Champaign
Urbana, Illinois
FY 1990 $162,865

The actions of progesterone, a hormone of central importance in controlling the function and growth of female reproductive tissues such as breast and uterus, appear to be mediated via interaction with an intracellular protein, the progesterone receptor (PR). Although much is known about the nature of this protein, little is known about the synthesis and degradation of PR and factors that regulate these rates. Initial studies have provided evidence for a biosynthetic, non hormone-binding precursor of PR and for differences in the form of PR when it is associated with the antiprogestin RU 486 vs progestin. The aims of this research are to study hormonal factors involved in regulation of PR levels and turnover, to investigate biosynthetic precursors of PR, and to examine the nature of nuclear PR complexes. These studies should provide new information on the biosynthesis and degradation of this important regulatory protein, and on the receptor interactions that may underlie progestin antagonist action.

NATIONAL CENTER FOR RESEARCH RESOURCES

The National Center for Research Resources (NCRR) supports research involving RU 486 through the General Clinical Research Center (GCRC) mechanism. This center grant program supplies funds for critical core resources which provide support for an array of research "subprojects" in each center. Both of the GCRC subprojects involving RU 486 are studying disorders resulting from the abnormal growth of reproductive tissues.

MO1 RR00827 General Clinical Research Center

Yen, Samuel University of California San Diego
San Diego, California
FY 1990 $19,951

NCRR (continued)

Subproject 0385 - Treatment of Pelvic Endometriosis with RU 486

The primary purpose of this subproject is to determine the biologic effects of the use of RU 486 as a treatment for pelvic endometriosis. In addition, this subproject will contribute to an evaluation of the long-term effects of RU 486 on the hypothalamic-pituitary-ovarian/adrenal axes.

Subproject 0403 - Treatment of Uterine Leiomyoma with RU 486

This subproject will seek to determine the biologic effects of the use of RU 486 as a treatment for uterine leiomyoma (fibroids). The effectiveness will be assessed in patients by pelvic exam and ultrasonography. This subproject will also support the evaluation of the long-term effects of RU 486 on the hypothalamic-pituitary-ovarian/adrenal axes.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Research involving RU 486 supported or conducted by the National Institute of Child Health and Human Development (NICHD) has continued to focus on both the antiglucocorticoid and antiprogesterone properties of the drug. This research has included both extramural research (supported at other institutions) and intramural studies (research conducted by NICHD scientists).

Extramural Research

RO1 HD26181 Myometrial Gap Junction Modulation in Preterm Labor

Larsen, William J. University of Cincinnati
Cincinnati, Ohio
$112,479

Preterm labor is a major cause of infant mortality in the United States and results in major medical expenditures for the care of surviving infants. The successful design of therapies to prevent preterm labor in patients at risk or to inhibit preterm myometrial contractions once they have begun requires a greater understanding of the cellular mechanisms which underlie human preterm labor. One pivotal cellular event in the cascade which brings about productive myometrial contractions in both preterm and normal labor is the rapid and dramatic development of a functional population of myometrial gap junctions in the final 24-72 hours prior to parturition. Shortly after parturition this population of gap junctions disappears. Although this relationship has been well established in a wide variety of species, including the human, and general hormonal controls have been investigated, much useful information regarding relationships between gap junction protein metabolism, gap junction assembly and their removal from the membrane.

NICHD (continued)

and the development of synchronous contractile activity remains to be elucidated. Studies with animals will be carried out over a wide time course with particular attention to the final 96 hours prior to delivery. These relationships will then be compared to those occurring in several different other animal models of preterm labor including the ovariectomized rat, and in animals injected with estradiol, RU 486, prostaglandins and indomethacin. Data obtained in these studies should provide a fundamental basis for the development of new preventive therapies and risk assessments for preterm labor.

Intramural Research

The NICHD intramural research program has continued to conduct both laboratory and clinical studies exploring the physiologic actions and effects of RU 486, and using it as a tool to block the normal action of glucocorticoids and progesterone in order to understand the normal actions of these hormones in the body. It is not possible to assign specific costs to these projects in the intramural program.

Developmental Endocrinology Branch (DEB)

DEB Animal Studies

The ability of daily administration of RU 486 to block implantation was assessed in the guinea pig. The compound prevented pregnancy in normally cycling sexually active females. The study is completed, and a manuscript has been submitted for publication.

DEB Human Studies

The studies of RU 486 in humans conducted by the DEB have continued to include physiologic studies of the effects of RU 486 on secretion of gonadotropins and sex steroids in both men and women and its effect on the endometrium of normally cycling women.

All women enrolled in these studies are counselled regarding the risk of abortion following RU 486 administration in early pregnancy. All sexually active women participants must use some form of nonhormonal birth control, such as barrier methods, IUD or sterilization methods, during the studies. In addition, all women subjects must have a negative pregnancy test prior to RU 486 administration.

Protocol 83-CH-87	Therapy of Patients with Cushing's Syndrome Due to Metastatic Adrenocortical Carcinoma or Ectopic ACTH Syndrome with the Glucocorticoid Antagonist (Antiglucocorticoid) RU 486.
Chrousos, George	NIH-NICHD-DEB Bethesda, Maryland

NICHD (continued)

Cushing's syndrome is a condition which results from excessive production of the adrenal gland hormone, cortisol. Excessive amounts of this hormone cause numerous abnormalities of body tissues and blood chemistry. This can lead to conditions such as obesity, leg and arm muscle weakness, hypertension, and thinning of the skin with stretch marks or easy bruising. The drug RU 486 has been shown to have the capacity to block the action of cortisol. This has helped to correct the tissue abnormalities caused by excessive cortisol production. This study, recently completed, showed the safety and effectiveness of RU 486 to treat the signs and symptoms of Cushing's syndrome, and determined the drug dose needed to treat this disorder.

As the result of this success, the protocol was extended to include therapeutic use of RU 486 in blocking the effects of cortisol to patients being prepared for surgery as treatment for Cushing's Syndrome. Surgery is particularly hazardous for patients with Cushing's Syndrome, and the use of RU 486 to correct the abnormalities caused by excess cortisol before surgery has been shown to make the procedure safer and improve outcome.

Protocol 83-CH-223 — Effects of RU 486 on Gonadotropin and Sex Steroid Secretion in Normal Men and Women

Nieman, Lynnette — NIH-NICHD-DEB
Bethesda, Maryland

The function of progesterone has not been clearly defined. In men, postmenopausal women, and in women during the follicular phase of the menstrual cycle, in whom blood levels are low and invariant, the hormone is said to have little physiologic impact. Hypotheses regarding the role of progesterone in women have been formulated on the basis of the temporal association of changes in plasma progesterone concentrations with changes in gonadotropin secretion patterns, body temperature and endometrial histology. Until recently, these hypotheses could only be tested by inference, by castration, or by administering exogenous progesterone. With the advent of the progesterone antagonist RU 486, there is now a way to examine the effect of progesterone on gonadotropin and steroid secretion by selectively blocking its biologic action.

This completed protocol compared 24 hour gonadotropin and sex steroid secretion patterns in women and men before and after RU 486 administrations. In women, the hormonal profile of the entire cycle was characterized. In men, steroid products and precursors were measured to evaluate the possible direct effects of the drug on synthetic pathways in the adrenal gland and testis.

Early results of these studies were reported in the New England Journal of Medicine on January 22, 1987. Final data are being analyzed for future publication.

NICHD (continued)

Protocol 86-CH-194 — Effects of RU 486 - Endometrial Morphology in Normally Cycling Women

Nieman, Lynnette — NIH-NICHD-DEB
Bethesda, Maryland

This protocol is designed to evaluate the effects of a small daily dose of RU 486 (10 mg/day or less for the first 26 days of the cycle) on endometrial morphology. Since progesterone is essential for the development of a secretory endometrium, small doses of a progestrone antagonist may prevent normal development of a secretory endometrium, and so may render a woman infertile.

The hormonal profiles of three menstrual cycles will be characterized. The first cycle is a pretreatment cycle; the second is a treatment cycle during which either RU 486 (up to 10 mg daily dose from days 1-26) or placebo will be taken by mouth; the third cycle is a post-treatment cycle. An endometrial biopsy will be performed during the second cycle to evaluate the effect of the drug on the endometrium. Eleven women have completed the initial protocol. RU 486 at a daily dose of 1 mg delayed endometrial maturation without significantly altering gonadotropin or sex steroid production.

This protocol has been modified to include daily ultrasound examination of the ovaries to evaluate follicular development and ovulation. Also, cervical mucus will be evaluated at midcycle. These changes are designed to examine the effects of RU 486, at a 1 mg/day dose, on folliculogenesis and cervical mucus.

Protocol 83-CH-146 — Effects of the Glucocorticoid Antagonist RU 486 on Immune Function in Normal Volunteers and Patients with Hypercortisolism

Laue, Louisa — NIH-NICHD-DEB
Bethesda, Maryland

The antiglucocorticoid effects of RU 486 on immune function in normal volunteers and patients with hypercortisolism were evaluated in this protocol. A randomized cross-over study design was used in which men

received RU 486 (10 mg/kg/day) or placebo for 14 days, followed by a 14 day "rest," followed by a 14 day treatment with the second agent (drug or placebo). Leukophoresis was performed during each treatment to evaluate the effects on circulating white blood cells. A manuscript describing this study and its results has been prepared and submitted for publication.

NICHD (continued)

Endocrinology and Reproduction Research Branch (ERRB)

Direct Action of the Antiprogestin RU 486 on Human Trophoblast

Das, Chandra — NIH-NICHD-ERRB, Bethesda, Maryland

The in vitro effects of RU 486 on placental production of human chorionic gonadotropin, prolactin, and progesterone were studied in different types of cells obtained from term human placenta. These studies indicated that RU 486 can inhibit secretion of all these hormones. These findings also indicate that the syncytiotrophoblast contains receptors for progesterone, that progesterone has a supportive role in several of the secretory functions of the human placenta, and that the blocking action of RU 486 might be useful in inducing labor at term or in post-term pregnancy. This study was published in The Lancet of September 12, 1987.

City of New York
CONSUMER AFFAIRS

Mark Green
Commissioner
80 Lafayette Street
New York, NY 10013

STATEMENT OF MARK GREEN
COMMISSIONER, DEPARTMENT OF CONSUMER AFFAIRS
NEW YORK CITY
NOVEMBER 19, 1990

Chairman Wyden,

Mayor Dinkins has directed me and city health officials to determine how to make sure that American women have no less contraceptive choice than French women.

Consequently, we are beginning meetings today with interested health professionals, community activists, feminists, and clergy to develop a strategy that could ultimately bring RU-486 into this country to be tested and marketed.

It is outrageous that political pressure is keeping an apparently safe, effective, and desired drug out of the hands of American women. If Roussel UCLAF refuses to export RU-486 because of the "political climate" around abortion, pro-health public officials must try to change that climate. And if the Bush Administration and the FDA continue to be anti-choice and anti-science, a Congressional-State-Urban alliance will have to convince Hoechst that what they could earn in profits outweighs what they might lose from boycotts.

Consequently, the City of New York looks forward to working with you and your Committee to see that that informed choice triumphs over ignorance and that American consumers have the contraceptive options that they need and deserve.

JANE GREENBERG A PROFESSIONAL CORPORATION
ATTORNEY AT LAW

JANE GREENBERG*
*N.J. and Ky. Bars

7008 BOULEVARD EAST
GUTTENBERG, NEW JERSEY 07093

TEL: (201) 868-2607
FAX: (212) 268-0469

November 13, 1990
Fax Comm. (202) 225-8941

Congressman Ron Wyden, Chairman
United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Energy
B-363 Rayburn House Office Bldg.
Washington, DC 20515

Dear Chairman Wyden:

I want to take this opportunity to apologize for not being able to be present in person at what I consider a most important hearing due to circumstances beyond my control. However, I am taking this means to add my voice and the voice of my two daughters and their twin baby girls who genetically are at great risk for breast cancer. Realizing that each year breast cancer claims the lives of many women (43,000 alone

this year) as it did my own mother's life.

Now to my testimony in answer to your questions.

(1) In 1987 I was diagnosed as having breast cancer of the minor invasive type which threatened the left breast as well, since the carcinoma was located in my right breast. After the traumatic diagnosis, I went to four different physicians and received opinions for treatment that varied from a double radical mastectomy to a lumpectomy of the right breast only followed by radiation treatment. I chose the lumpectomy and radiation course of treatment and hoped for the best. After a year and a half I learned through an article in the New York Times as well as other literature of the success of Dr. Ezra Greenspan use of Tamoxifen. I secured an appointment with Dr. Greenspan and am still on Tamoxifen therapy. Before the Tamoxifen therapy

I underwent a grueling six months of chemotherapy:

(2) Naturally, my life was completely disrupted and dramatically changed both physically and emotionally by the surgeries, radiation, and chemotherapy, that there came a time that I could no longer function in my position and was forced to go on disability. Of course, I must constantly live with the fear of the recurrance of the cancer to my left breast or its metastasis to some other part of my body.

(3) I have learned that an informed patient can best help themselves by keeping abreast of all the current material pertinent to their disease. In the November, 1990, of the magazine Longevity, I read with avid interest the article written by Carol Kahn about RU-486 and its potential help in advanced breast cancer patients. I then called Dr. William Regelson, who was mentioned

in the article, to see how I might obtain more information about RU-486 and how it might help me.

It is essential to every cancer survivor that there be alternative breast cancer therapies in the event one's current therapy should no longer prove successful. The research and development of alternative breast cancer therapies is the prayer of every cancer survivor.

(4) It is obvious to me that the research on RU-486 as it relates to the treatment of breast cancer should absolutely continue in the United States. I think it should be a moral imperative that the United States Government should do everything in its power to ensure the eradication of this dreaded disease, and if RU-486 should turn out to be one of those vehicles then it would be criminal to inhibit further investigation of its possibilities regardless of any other political considerations.

This is a health issue, not a political issue.

Sincerely yours,

Jane Kirkpatrick Dreesbach

P.S. I would also like to indicate at this point that my husband is also recovering from lung cancer, which was operated on and removed in 1987, and we can never tell what RU-486 trials could ultimately lead — even to all cancers.

STATEMENT OF JANE KIRKPATRICK GREENBERG
SUBMITTED BEFORE THE
SMALL BUSINESS SUBCOMMITTEE ON
REGULATION, BUSINESS OPPORTUNITIES AND ENERGY

NOVEMBER 19, 1990
* * *

I wanted to take this opportunity to apologize for not being able to be present in person, at what I consider a most important hearing, due to circumstances beyond my control. However, I am taking this means to add my voice and the voices of my two daughters ant their twin baby girls who genetically are at great risk from breast cancer. Realizing that each year breast cancer claims the lives of many women (43,000 alone this year) as it did my own mother's life.

Now, to my testimony in answer to your questions:

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This is a health issue, not political issue.

Sincerely yours,

Jane Kirkpatrick Greenberg

P.S.: I would also like to indicate at this point that my husband is also recovering from lung cancer, which was operated on and removed in 1987, and one can never tell where RU 486 trials could ultimately lead -- even to all cancers.

NABCO

NATIONAL ALLIANCE
OF BREAST CANCER
ORGANIZATIONS

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Founding Executive Director
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Ruth Spear

Second Floor
1180 Avenue of the Americas
New York, N.Y. 10036
212-719-0154

November 16, 1990

The Hon. Ron Wyden, Chairman
United States House of Representatives
Committee on Small Business
Subcommittee On Regulation, Business
Opportunities and Energy
B-363 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman:

On behalf of our 220 member organizations caring for hundreds of thousands of breast cancer patients, the National Alliance of Breast Cancer Organizations (NABCO) wishes to submit for the record certain information relevant to your Committee's November 19, 1990 hearing on access to the drug RU-486 for research purposes. NABCO is a non-profit, central resource of information about the detection and treatment of breast cancer, and acts as an advocate for the rights and concerns of breast cancer patients and their families.

Breast cancer is the most common form of cancer in American women. In 1990, the American Cancer Society estimates that 150,000 women will be diagnosed with the disease; 44,000 will die from it. Currently, one in 10 American women will develop breast cancer in her lifetime, and its incidence continues to increase. The overall five year survival rate for breast cancer is 75% (90% if diagnosed and treated in its earliest stages)*. The National Cancer Institute has estimated the annual cost of cancer in the United States at $83.5 billion**. If we assume that breast cancer's costs are in proportion to breast cancer's percentage of total annual cancer diagnoses, its annual cost would exceed $12 billion.

Despite advances in surgical management and systemic treatment for the disease, the breast cancer mortality rate has changed little in the past 20 years. Scientists do not know what causes breast cancer, and no current treatment assures its cure: breast cancer can recur as long as thirty years after its initial diagnosis. Until a cure is found, improvements in systemic treatment for breast cancer offer women their best hope for long life, with a high quality of life, after diagnosis.

I refer to "systemic" treatments because of the current perception of the mechanism of breast cancer. Until as recently as fifteen years ago, surgery was the primary means of managing the disease: it was thought that a radical excision of the tumor with surrounding breast skin and tissue, chest muscles and regional lymphatics was the approach that was most likely to eradicate the disease. However, as women continued to recur and die from metastatic disease after this disfiguring surgery, physicians began to revise their conception of the disease.

This shift in the understanding of breast cancer from being a disease with a local manifestation (usually a breast mass) needing local management to being a local manifestation often accompanied by microscopic malignancies elsewhere in the body

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* Cancer Facts & Figures - 1990, American Cancer Society.
** NCI Fact Book, 1989 edition, p. 37. Cost data as of 1987.

has led to a shift in the protocols for treatment. Local control is now achieved by excision of the breast mass and axillary lymph nodes followed by radiation therapy, or by simple removal of the breast and nodes. Increasingly, for all but the tiniest Stage I tumors with no evidence of nodal involvement, experts recommend adjuvant (prophylactic) treatment with systemic chemotherapy and hormonal agents, employed to halt or delay the progress of micrometastases into a recurrence. If a patient does recur, different combinations of these and similar agents are used in an attempt to eradicate her disease.

The biomechanisms of breast cancer include its frequent tendency to respond to the presence or absence of natural or synthetic estrogen and estrogenic agents. For this reason, protocols used in the treatment of breast cancer often employ estrogen antagonists. The drug most commonly used in hormonal therapy for breast cancer is tamoxifen, an anti-estrogen which acts as a tumorstatic agent, interrupting a cell's ability to take in the estrogen which would fuel its growth.

The drug which is the subject of your hearing, RU-486, is an anti-progesterone, acting in a similar fashion to tamoxifen in its manipulation of the cell's hormonal access. Tamoxifen has been widely prescribed in America and abroad, and has been demonstrated to be highly effective in delaying recurrence and prolonging patient survival in the adjuvant setting, as well as being an effective, well-tolerated agent in the treatment of progressive disease.

Not all patients respond to tamoxifen, however, so the search for chemically similar agents with similar risks and benefits, but which may act differently enough to help these patients, has great logic and merit. We are familiar with two preliminary studies examining the potential efficacy of RU-486 in treating breast cancer, both from European investigators. Both have indicated encouraging results, and clearly suggest that further research would be beneficial. Each day in which supplies of promising agents are withheld from American researchers, 120 American women die from breast cancer.

You have asked for our views regarding the safety of RU-486. This is a circular problem--it is NABCO's position that all agents showing promise in the treatment of breast cancer should be accessible to qualified researchers conducting initial, and then clinical, trials. These trials, if properly designed and implemented, have the express purpose of evaluating drug safety and efficacy. Without the drug, there cannot be trials. The ultimate goal for an effective breast cancer drug would be that, like tamoxifen, this drug would be selected and prescribed or administered by a qualified physician, who would subsequently supervise and monitor the patient.

You have also asked whether NABCO is aware of any effects that the RU-486 controversy may have had on access to other similar drugs that are potentially useful for breast cancer research. We are not. If other foreign manufacturers are now hesitant to supply promising drugs to United States researchers, this would cause us great concern. Breast cancer research is truly an international discipline: at the recent San Antonio Breast Cancer Symposium, one of the field's most important annual conferences, by my count presentations were made by researchers from at least twelve foreign countries. Worldwide access to information and treatment agents is necessary in order to answer the pivotal unanswered questions leading to the cause of, and cure for, this disease.

There are a limited number of avenues to ameliorate the critical public health problem that breast cancer has become, and Americans require governmental support for each. In terms of early detection, it is only this year that we have seen Federal legislation that recognizes the importance of screening mammography: the abbreviated Medicare screening coverage and the CDC grant for screening the underserved are long overdue. Federal breast cancer research funding, historically small in proportion

to the large number of diagnoses and deaths, now must compete with a newer epidemic. Access to promising investigational treatments for breast cancer has been slowed or stopped by regulatory requirements. You now must decide whether the RU-486 roadblock will be removed or if it will stand, along with the others to which breast cancer patients have become accustomed. It is our position that properly-conducted U.S.investigations of the use of RU-486 as a treatment for breast cancer should be made possible, and this requires providing access to the drug.

Thank you for the opportunity to comment on this vitally important subject.

Very truly yours,

Amy S. Langer
Executive Director